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OF ORGANIC CHEMICALS

VOLUME 77

2000

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ORGANIC
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OF ORGANIC COMPOUNDS
VOLUME 11

The procedures in this text are intended for use only by persons with prior training in the field of organic chemistry. In the checking and editing of these procedures, every effort has been made to identify potentially hazardous steps and to eliminate as much as possible the handling of potentially dangerous materials; safety precautions have been inserted where appropriate. If performed with the materials and equipment specified, in careful accordance with the instructions and methods in this text, the Editors believe the procedures to be very useful tools. However, these procedures must be conducted at one's own risk. Organic Syntheses, Inc., its Editors, who act as checkers, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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NOTICE

With Volume 62, the Editors of *Organic Synthesis* began a new presentation and distribution policy to shorten the time between submission and appearance of an accepted procedure. The soft cover edition of this volume is produced by a rapid and inexpensive process, and is sent at no charge to members of the Organic Divisions of the American and French Chemical Society, The Perkin Division of the Royal Society of Chemistry, and The Society of Synthetic Organic Chemistry, Japan. The soft cover edition is intended as the personal copy of the owner and is not for library use. A hard cover edition is published by John Wiley & Sons, Inc. in the traditional format, and differs in content primarily in the inclusion of an index. The hard cover edition is intended primarily for library collections and is available for purchase through the publisher. Annual Volumes 70–74 have been incorporated into a new five-year version of the collective volumes of *Organic Syntheses* which has appeared as *Collective Volume Nine* in the traditional hard cover format. It is available for purchase from the publishers. The Editors hope that the new *Collective Volume* series, appearing twice as frequently as the previous decennial volumes, will provide a permanent and timely edition of the procedures for personal and institutional libraries. The Editors welcome comments and suggestions from users concerning the new editions.

NOMENCLATURE

Both common and systematic names of compounds are used throughout this volume, depending on which the Editor-in-Chief felt was more appropriate. The *Chemical Abstracts* indexing name for each title compound, if it differs from the title name, is given as a subtitle. Systematic *Chemical Abstracts* nomenclature, used in both the recent Collective Indexes for the title compound and a selection of other compounds mentioned in the procedure, is provided in an appendix at the end of each preparation. Registry numbers, which are useful in computer searching and identification, are also provided in these appendixes. Whenever two names are concurrently in use and one name is the correct *Chemical Abstracts* name, that name is preferred.

SUBMISSION OF PREPARATIONS

Organic Synthesis welcomes and encourages submission of experimental procedures which lead to compounds of wide interest or which illustrate important new developments in methodology. The Editorial Board will consider proposals in outline format as shown below, and will request full experimental details for those proposals which are of sufficient interest. Submissions which are longer than three steps from commercial sources or from existing *Organic Syntheses* procedures will be accepted only in unusual circumstances.

Organic Synthesis Proposal Format

- 1) Authors
- 2) Title
- 3) Literature reference or enclose preprint if available
- 4) Proposed sequence
- 5) Best current alternative(s)
- 6) a. Proposed scale, final product:
 - b. Overall yield:
 - c. Method of isolation and purification:
 - d. Purity of product (%):
 - e. How determined?

- 7) Any unusual apparatus or experimental technique?
- 8) Any hazards?
- 9) Source of starting material?
- 10) Utility of method or usefulness of product

Submit to: Dr. Jeremiah P. Freeman, Secretary
Department of Chemistry
University of Notre Dame
Notre Dame, IN 46556

Proposals will be evaluated in outline form, again after submission of full experimental details and discussion, and, finally by checking experimental procedures. A form that details the preparation of a complete procedure (Notice to Submitters) may be obtained from the Secretary.

Additions, corrections, and improvements to the preparations previously published are welcomed; these should be directed to the Secretary. However, checking of such improvements will only be undertaken when new methodology is involved. Substantially improved procedures have been included in the Collective Volumes in place of a previously published procedure.

ACKNOWLEDGMENT

Organic Synthesis wishes to acknowledge the contributions of ArQule, Hoffmann-La Roche, Inc. and Merck & Co. to the success of this enterprise through their support, in the form of time and expenses, of members of the Boards of Directors and Editors.

HANDLING HAZARDOUS CHEMICALS

A Brief Introduction

General Reference: *Prudent Practices in the Laboratory*; National Academy Press; Washington, DC, 1995.

Physical Hazards

Fire. Avoid open flames by use of electric heaters. Limit the quantity of flammable liquids stored in the laboratory. Motors should be of the nonsparking induction type.

Explosion. Use shielding when working with explosive classes such as acetylides, azides, ozonides, and peroxides. Peroxidizable substances such as ethers and alkenes, when stored for a long time, should be tested for peroxides before use. Only sparkless “flammable storage” refrigerators should be used in laboratories.

Electric Shock. Use 3-prong grounded electrical equipment if possible.

Chemical Hazards

Because all chemicals are toxic under some conditions, and relatively few have been thoroughly tested, it is good strategy to minimize exposure to all chemicals. In practice this means having a good, properly installed hood; checking its performance periodically; using it properly; carrying out most operations in the hood; protecting the eyes; and, since many chemicals can penetrate the skin, avoiding skin contact by use of gloves and other protective clothing.

a. Acute Effects. These effects occur soon after exposure. The effects include burn, inflammation, allergic responses, damage to the eyes, lungs, or nervous system (e.g., dizziness), and unconsciousness or death (as from overexposure to HCN). The effect and its cause are usually obvious and so are the methods to prevent it. They generally arise from inhalation or skin con-

tact, so should not be a problem if one follows the admonition “work in a hood and keep chemicals off your hands”. Ingestion is a rare route, being generally the result of eating in the laboratory or not washing hands before eating.

b. Chronic Effects. These effects occur after a long period of exposure or after a long latency period and may show up in any of numerous organs. Of the chronic effects of chemicals, cancer has received the most attention lately. Several dozen chemicals have been demonstrated to be carcinogenic in man and hundreds to be carcinogenic to animals. Although there is no simple correlation between carcinogenicity in animals and in man, there is little doubt that a significant proportion of the chemicals used in laboratories have some potential for carcinogenicity in man. For this and other reasons, chemists should employ good practices.

The key to safe handling of chemicals is a good, properly installed hood, and the referenced book devotes many pages to hoods and ventilation. It recommends that in a laboratory where people spend much of their time working with chemicals there should be a hood for each two people, and each should have at least 2.5 linear feet (0.75 meter) of working space at it. Hoods are more than just devices to keep undesirable vapors from the laboratory atmosphere. When closed they provide a protective barrier between chemists and chemical operations, and they are a good containment device for spills. Portable shields can be a useful supplement to hoods, or can be an alternative for hazards of limited severity, e.g., for small-scale operations with oxidizing or explosive chemicals.

Specialized equipment can minimize exposure to the hazards of laboratory operations. Impact resistant safety glasses are basic equipment and should be worn at all times. They may be supplemented by face shields or goggles for particular operations, such as pouring corrosive liquids. Because skin contact with chemicals can lead to skin irritation or sensitization or, through absorption, to effects on internal organs, protective gloves are often needed.

Laboratories should have fire extinguishers and safety showers. Respirators should be available for emergencies. Emergency equipment should be kept in a central location and must be inspected periodically.

DISPOSAL OF CHEMICAL WASTE

General Reference: *Prudent Practices in the Laboratory*, National Academy Press, Washington, D.C. 1995

Effluents from synthetic organic chemistry fall into the following categories:

1. Gases

- 1a. Gaseous materials either used or generated in an organic reaction.
- 1b. Solvent vapors generated in reactions swept with an inert gas and during solvent stripping operations.
- 1c. Vapors from volatile reagents, intermediates and products.

2. Liquids

- 2a. Waste solvents and solvent solutions of organic solids (see item 3b).
- 2b. Aqueous layers from reaction work-up containing volatile organic solvents.
- 2c. Aqueous waste containing non-volatile organic materials.
- 2d. Aqueous waste containing inorganic materials.

3. Solids

- 3a. Metal salts and other inorganic materials.
- 3b. Organic residues (tars) and other unwanted organic materials.
- 3c. Used silica gel, charcoal, filter aids, spent catalysts and the like.

The operation of industrial scale synthetic organic chemistry in an environmentally acceptable manner* requires that all these effluent categories be dealt with properly. In small scale operations in a research or academic set-

*An environmentally acceptable manner may be defined as being both in compliance with all relevant state and federal environmental regulations *and* in accord with the common sense and good judgement of an environmentally aware professional.

ting, provision should be made for dealing with the more environmentally offensive categories.

- 1a. Gaseous materials that are toxic or noxious, e.g., halogens, hydrogen halides, hydrogen sulfide, ammonia, hydrogen cyanide, phosphine, nitrogen oxides, metal carbonyls, and the like.
- 1c. Vapors from noxious volatile organic compounds, e.g., mercaptans, sulfides, volatile amines, acrolein, acrylates, and the like.
- 2a. All waste solvents and solvent solutions of organic waste.
- 2c. Aqueous waste containing dissolved organic material known to be toxic.
- 2d. Aqueous waste containing dissolved inorganic material known to be toxic, particularly compounds of metals such as arsenic, beryllium, chromium, lead, manganese, mercury, nickel, and selenium.
3. All types of solid chemical waste.

Statutory procedures for waste and effluent management take precedence over any other methods. However, for operations in which compliance with statutory regulations is exempt or inapplicable because of scale or other circumstances, the following suggestions may be helpful.

Gases

Noxious gases and vapors from volatile compounds are best dealt with at the point of generation by "scrubbing" the effluent gas. The gas being swept from a reaction set-up is led through tubing to a (large!) trap to prevent suck-back and on into a sintered glass gas dispersion tube immersed in the scrubbing fluid. A bleach container can be conveniently used as a vessel for the scrubbing fluid. The nature of the effluent determines which of four common fluids should be used: dilute sulfuric acid, dilute alkali or sodium carbonate solution, laundry bleach when an oxidizing scrubber is needed, and sodium thiosulfate solution or diluted alkaline sodium borohydride when a reducing scrubber is needed. Ice should be added if an exotherm is anticipated.

Larger scale operations may require the use of a pH meter or starch/iodide test paper to ensure that the scrubbing capacity is not being exceeded.

When the operation is complete, the contents of the scrubber can be poured down the laboratory sink with a large excess (10–100 volumes) of water. If the solution is a large volume of dilute acid or base, it should be neutralized before being poured down the sink.

Liquids

Every laboratory should be equipped with a waste solvent container in which *all* waste organic solvents and solutions are collected. The contents of these containers should be periodically transferred to properly labeled waste solvent drums and arrangements made for contracted disposal in a regulated and licensed incineration facility.**

Aqueous waste containing dissolved toxic organic material should be decomposed *in situ*, when feasible, by adding acid, base, oxidant, or reductant. Otherwise, the material should be concentrated to a minimum volume and added to the contents of a waste solvent drum.

Aqueous waste containing dissolved toxic inorganic material should be evaporated to dryness and the residue handled as a solid chemical waste.

Solids

Soluble organic solid waste can usually be transferred into a waste solvent drum, provided near-term incineration of the contents is assured.

Inorganic solid wastes, particularly those containing toxic metals and toxic metal compounds, used Raney nickel, manganese dioxide, etc. should be placed in glass bottles or lined fiber drums, sealed, properly labeled, and arrangements made for disposal in a secure landfill.** Used mercury is particularly pernicious and small amounts should first be amalgamated with zinc or combined with excess sulfur to solidify the material.

Other types of solid laboratory waste including used silica gel and charcoal should also be packed, labeled, and sent for disposal in a secure landfill.

Special Note

Since local ordinances may vary widely from one locale to another, one should always check with appropriate authorities. Also, professional disposal services differ in their requirements for segregating and packaging waste.

**If arrangements for incineration of waste solvent and disposal of solid chemical waste by licensed contract disposal services are not in place, a list of providers of such services should be available from a state or local office of environmental protection.

PREFACE

This volume of *Organic Syntheses* provides 28 checked and edited experimental procedures that describe the preparation of useful chemicals and/or illustrate important new synthetic methods. This compilation of procedures has been organized according to the following broad areas: (a) reagents and procedures for asymmetric synthesis (b) useful processes (c) useful reagents and (d) useful compounds.

The volume begins with a series of ten procedures broadly related to the field of asymmetric synthesis. Asymmetric catalytic hydrogenation using a BINAP-ruthenium catalyst is featured in the preparation of **(R,R)-1,2:4,5-DIEPOXPENTANE**, a useful intermediate for the synthesis of anti-1,3-diols. The next procedure describes the preparation of **[R-(R*,S*)]- β -METHYL- α -PHENYL-1-PYRROLIDINEETHANOL**, a member of a class of amino alcohol ligands emerging as chiral mediators for the enantioselective addition of acetylides to prochiral ketones. The next four procedures revolve around the theme of chiral auxiliaries in asymmetric synthesis. The **DIASTEREOSELECTIVE ALKYLATION OF PSEUDOEPHEDRINE AMIDES** has emerged as the first step in methods for the **PREPARATION OF ENANTIOMERICALLY ENRICHED ALDEHYDES, ALCOHOLS, AND KETONES**. This overall process is illustrated with two procedures that provide **(R)- α -METHYLBENZENEPROPANAL**, **(R)- β -METHYLBENZENEPROPANOL**, and **(R)-2-METHYL-1-PHENYL-3-HEPTANONE** on a multi-gram scale. The use of **(R)-2-HYDROXY-1,2,2-TRIPHENYLETHYL ACETATE** as a reagent for the enantioselective synthesis of β -hydroxyacids has been previously described in Volume 72 of *Organic Syntheses*. An alternative method for the preparation of the reagent **[(R)-HYTRA]** that features a scandium(III) triflate-catalyzed esterification is described in this volume. The next procedure describes the preparation of the chiral sulfinimine **(S)-N-(BENZYLIDENE)-p-TOLUENESULFINAMIDE** and its reaction with the enolate derived from tert-butyl acetate to ultimately provide **METHYL (R)- β -PHENYLALANATE**. This procedure serves as a prototype for the use of sulfinimines as chiral azomethines in nucleophilic addition reactions. The next four procedures present syntheses of enantiopure compounds of general utility in asymmetric synthesis. The use of **1,1-DIMETHYLETHYL (S)-4-FORMYL-2,2-DIMETHYL-3-**

OXAZOLIDINECARBOXYLATE has previously been described in Volume 70 of *Organic Syntheses*. An alternative procedure for the preparation of this compound is presented in this volume along with its use in a diastereoselective addition reaction with **2-TRIMETHYLSILYLTHIAZOLE** to provide a compound bearing a 2-amino-1,3-diol substructure that appears in a variety of natural products. The conversion of abundantly available isosorbide into **O⁴,O⁵-ISOPROPYLIDENE-1,2:3,6-DIANHYDRO-D-GLUCITOL** provides a potentially useful carbohydrate-derived material for the use in complex tetrahydrofuran synthesis. Finally, asymmetric reduction of an α, β -unsaturated acylstannane with (R)-BINAL provides access to (S,E)-**1-(METHOXYMETHOXY)-1-TRIBUTYLSTANNYL-2-BUTENE**, an α -alkoxy allylstannane that has been used in enantioselective vicinal diol synthesis amongst other transformations.

The next four procedures describe synthetically useful processes. The first procedure describes the preparation of **MEHTYL 3-(HYDROXYMETHYL)-4-METHYL-2-METHYLENEPENTANOATE** via an allylindation reaction conducted in aqueous tetrahydrofuran. The starting material used for this procedure is prepared via a Baylis-Hillman reaction. This is followed by a general procedure for the synthesis of 2-alkyl-4-pyrones, such as **2-METHYL-4H-PYRAN-4-ONE**, from Meldrum's acid via a presumed acylketene-enol ether cycloaddition. Methodology for conducting photochemically-mediated higher order cycloaddition reactions is illustrated by the reaction of **TRICARBONYL(η^6 -CYCLOHEPTATRIENE)-CHROMIUM(O)** with 1-acetoxy-1,3-butadiene to give the [6+4] cycloadduct **7 α -ACETOXY-(1H β ,6H β)-BICYCLO[4.4.1]UNDECA-2,4,8-TRIENE**. This section concludes with a preparation of **2-(4'-ACETYL-PHENYL)THIOPHENE** that features a Stille coupling catalyzed by palladium-on-carbon with copper(I) iodide as a cocatalyst.

The next three procedures describe the preparation of reagents used to mediate useful transformations without being incorporated into the final product. The first of these reagents is **1,1,1-TRIACETOXY-1,1-DIHYDRO-1,2-BENZIODOXOL-3-(1H)-ONE**, the Dess-Martin periodinane. It is hoped that this will provide chemists with a reproducible procedure that provides 100-gram quantities of this valuable oxidizing agent. The preparation of **9-ETHYL-3,6-DIMETHYLCARBAZOLE** features a nickel mediated coupling of an aryl bromide with a Grignard reagent. This heterocyclic compound is a useful sensitizer for the selective **PHOTOCHEMICAL DEOXY-GENATION** of 3-trifluoromethyl benzoates, a process illustrated with a synthesis of the 2'-deoxyribonucleoside **3',5'-DI-O-BENZOYLTHYMIDINE**.

Reagents that deliver useful functionality in a variety of reactions are featured in the next five procedures. **BIS(PINACOLATO)DIBORON** is a

useful reagent for the synthesis of arylboronates, vinylboronates and allylboronates, compounds of great utility in carbon-carbon bond-forming reactions. **β -MERCAPTOPROPIONITRILE(2-CYANOETHANETHIOL)** provides an alternative to thioacetate as a reagent for introducing sulfur into molecules in a protected form. **α -TOSYLBENZYL ISOCYANIDE** is a versatile building block for the synthesis of a variety of heterocyclic compounds. **BIS(2,4,6-TRIMETHYLPYRIDINE)IODINE(I) HEXAFLUOROPHOSPHATE** and **BIS(2,4,6-TRIMETHYLPYRINE)BROMINE(I) HEXAFLUOROPHOSPHATE** serve as halogen sources for electrophile-initiated cyclizations reactions and other halogenations. The use of **6,6'-BI(3,4-DIHYDRO-2H-PYRAN)** as a reagent for the protection of transvicinal hydroxyl groups in carbohydrates is illustrated in the preparation of **METHYL 2,3-O-(6,6'-OCTAHYDRO-6,6'-BI-2H-PYRAN-2,2'-DIYL)- α -D-GALACTOPYRANOSIDE**.

The volume concludes with procedures describing the preparation of compounds that serve as starting points for the preparation of a variety of useful chemicals. **CYCLODEXTRIN MONOTOSYLATE (6^A-O-p-TOLUENESULFONYL- β -CYCLODEXTRIN)** provides access to modifications of the primary hydroxyl group side of this important host molecule. Two procedures for the preparation of this compound are described. **CYCLOPROPYLACETYLENE** is emerging as an important building block in the preparation of pharmaceuticals. Organic nitro compounds are useful intermediates for organic synthesis and the next procedure provides access to the bifunctional nitro compounds **3-NITROPROPANAL**, **3-NITROPROPANOL**, and **3-NITROPROPANAL DIMETHYL ACETAL**. The penultimate contribution to this volume of *Organic Syntheses* is a photochemical synthesis of **BICYCLO[1.1.1]PENTANE-1,3-DICARBOXYLIC ACID** that illustrates the use of [1.1.1]propellane as a starting material for the synthesis of bicyclo[1.1.1]pentanes. The final contribution describes an efficient synthesis of **CYCLOPROPENE** from allyl chloride, along with an example of its use as a dienophile in a Diels-Alder reaction.

Many people have contributed to this volume of *Organic Syntheses*. I thank the contributors for their development of the procedures contained in this volume, and my colleagues on the Editorial Board for their insight in soliciting contributions and their efforts to facilitate the checking process in a timely manner. I would particularly like to thank the coworkers of Editorial Board members, including my own students, for it is largely they who donated their time to carefully check, and in some cases improve, the procedures appearing in this volume. Finally I would like to thank Professor Jeremiah P. Freeman, who has served as Secretary to the Board for the last 20 years, and Theodora W. Greene, who has served as Assistant Editor for

the past 19 years. It is their constant hard work and effort that allowed this volume to be assembled in a timely and organized manner.

DAVID J. HART

Columbus, Ohio



GEORGE BÜCHI
August 1, 1921–August 28, 1998

The death of George Büchi on August 28, 1998, at the age of 77 deprives organic chemistry of one of its most gifted scientists and engaging personalities. The nearly 200 individuals who worked in his laboratory during his four decades as a faculty member in the Chemistry Department at MIT were the beneficiaries of a relationship which went well beyond that of mentor and student. Throughout his career, the driving force behind George's passion for chemistry was the pursuit of excellence—in all its forms—and the refined sense of aesthetics he imprinted on his students and even some of his colleagues distinguished him as a unique presence among the organic chemists of his time. George was a consummate stylist, he prized elegance above efficiency, and he leaves a body of work in the chemical literature which is an enduring reminder that research is a truly creative enterprise. In this respect, George's approach to chemistry, and particularly to synthesis, was closely aligned with the best of his chemical contemporaries, especially R. B. Woodward whom he admired immensely.

George Büchi was born in Baden, Switzerland, the son of an engineer who had spent a brief period in New York City installing the first steam-turbines at Hell's Gate. After receiving his Diploma in Chemical Engineer-

ing from ETH at the end of World War II, George continued his studies at ETH under Ruzicka, earning his doctorate in 1947. He then moved to the University of Chicago where he worked with Morris Kharasch as Firestone Postdoctoral Fellow. After three years in the U.S., the prospect of returning to an academic position in Switzerland seemed unappealing, and when an Assistant Professorship at MIT was offered, George acted promptly. His independent career blossomed immediately with simultaneous excursions into several areas of organic photochemistry. Indeed, the renaissance which took place in this field during the fifties can be traced in large measure to Büchi's seminal contributions. Yet, in spite of the discovery of an important photochemical reaction that now bears his name, George became disenchanted with photochemistry because, to quote from an interview he gave, "... useful applications were not forthcoming, and because the course of the transformations could rarely be predicted, thus robbing the investigator of the pleasure derived from designing new reactions."

However, it was not new reactions but rather the structural elucidation of new natural products that fascinated George Büchi for the next decade. Sesquiterpenes—patchoulol, maaliol, aromadendrene, valerianic acid, calarene, and copaene—and the alkaloids such as uleine, flavorcarpine, and (in association with Karl Wiesner) aconitine, all fell to his remarkable, intuitive insights into molecular structure. George had an extraordinary ability to see structural details invisible to lesser minds, and the graduate course he taught for many years on this subject at MIT was a classic. Those of us who took it will always remember the rigor and the sheer force of analytical reasoning that he brought to bear on the subject. The high point of this phase of George's career was undoubtedly the structure determination of aflatoxin B₁, a project initiated in 1963 with Gerald Wogan at MIT, which led to a long and fruitful research collaboration. This period witnessed the structural elucidation of some of the most complex mycotoxins known, including the rubratoxins, tryptoquivalines, and malformin C. George was at the forefront of all these ventures, and his laboratory was surely one of the world's most exciting research venues of the time. In all, the structures of some 55 natural products were correctly assigned as the result of research in George's group, most with spectroscopic tools that today would be regarded as primitive indeed.

The third and in many ways most creative phase of George Büchi's career had its roots in his doctoral work at ETH, where he had undertaken the synthesis of degradation products of certain triterpenes. Synthetic studies on natural products has always flourished in George's laboratory at MIT, but with his growing interest in complex alkaloid came the opportunity to ex-

ercise his talents in this rapidly developing field. George's syntheses of the iboga alkaloids vindoline and catharanthine are still considered landmarks in the field; as the citation for his Killian Award at MIT states, "His syntheses have been consistently notable for economy, elegance, and originality and have the style that characterizes today's organic synthesis." George's modesty would have led him to demur, but there is not doubt that this acclamation captures the essence of his approach to synthesis.

George, in fact, attached little significance to accolades. Even though he was the first recipient of the Ruzicka Prize of the Swiss Chemical Society, received both the Fritzche Award and the Award for Creative Work in Synthetic Organic Chemistry from the American Chemical Society, and was elected to the National Academy at the relatively young age of 44, it was the intellectual challenge of a chemical problem that truly excited him. For George, the satisfaction of a completed total synthesis for outweighed the gratification that honors could bestow.

George's scientific activities encompassed a variety of roles outside the purely academic domain, including a term of the Board of Editors of *Organic Syntheses* (he was Editor-in-Chief of Volume 56). During his term on the Board, he checked 44 preps submitted to *Organic Syntheses*—a record that still stands. For many years, he was a consultant to Firmenich SA in Geneva, and through his association with Firmenich, a number of commercially important fragrances such as muscone, methyl jasmonate, damascones, and khusimone were obtained by synthesis for the first time. He was also a long-time consultant for Hoffmann-LaRoche, and he leaves many friends in Nutley who remember his wise counsel as well as his encyclopedic knowledge of the chemical literature.

Throughout his life, George was an avid outdoorsman who traveled to many parts of the world in order to indulge his love of hunting and fishing. He often returned with substantial trophies to be hung in his office; these impressed visitors, but more importantly, they provided an opportunity for reluctant students to plan diversionary tactics when there was little research progress to report. In his youth, George had been an accomplished skier, and it was a broken leg incurred in a skiing accident which caused the limp associated with "GB" for as long as anyone can remember. With advancing age, this injury led to orthopedic problems which were partially ameliorated by a hip replacement. This enabled George to resume an active life, and it was while hiking a favorite trail in his beloved Swiss Alps with his wife, Anne, that George suffered his fatal heart attack. If there is any consolation in this sad event, it is that George Büchi died doing what he really enjoyed.

George Büchi is survived by Anne Barkman Büchi, his devoted wife of 43 years, and by his brother Heinrich of Bern, Switzerland.

JAMES D. WHITE

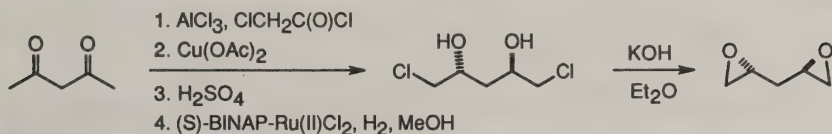
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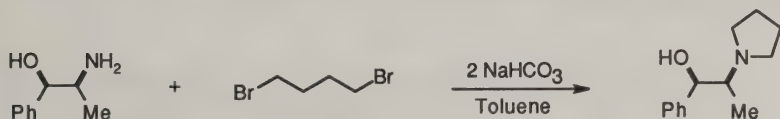
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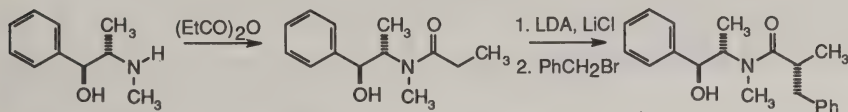
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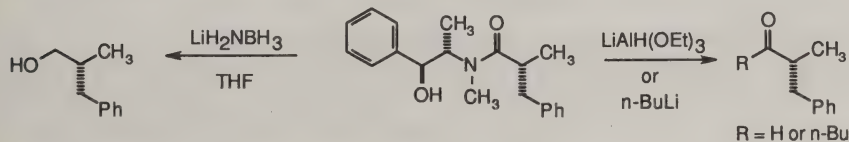
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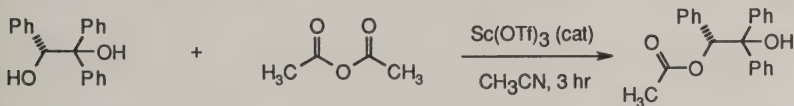
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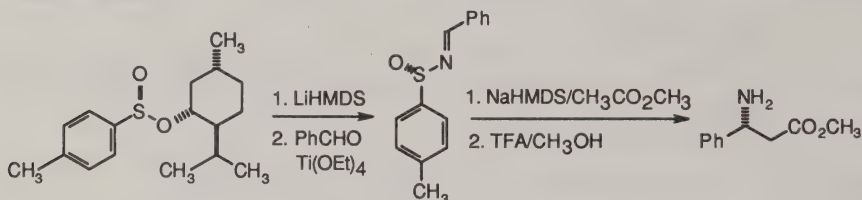
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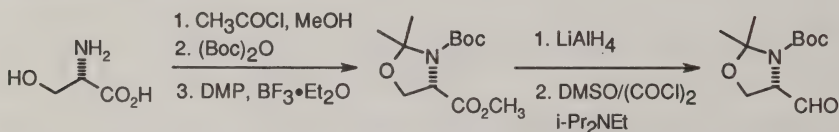
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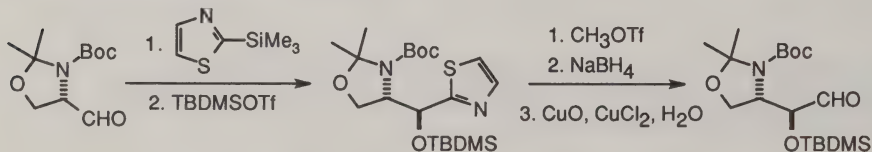
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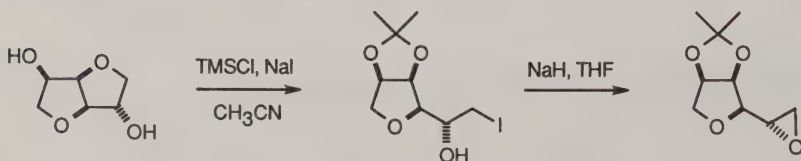
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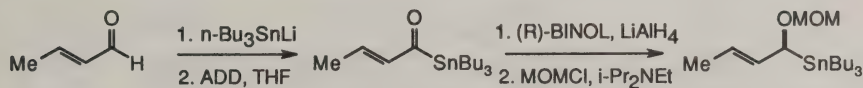
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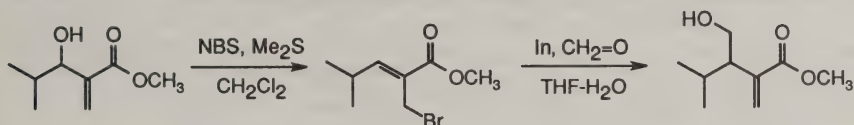
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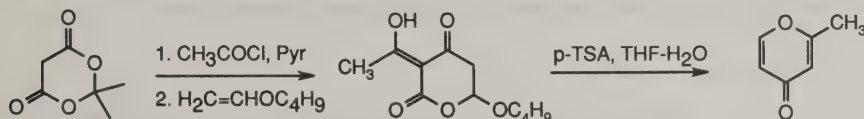
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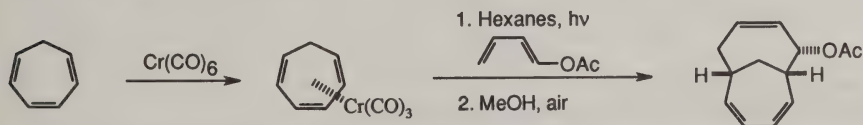
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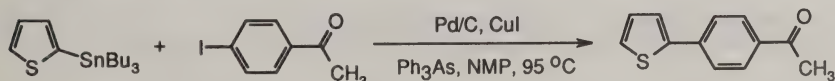
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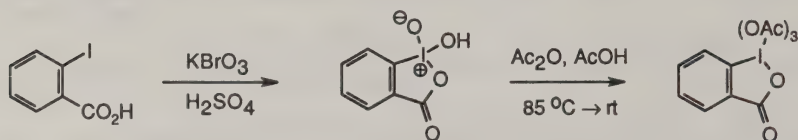
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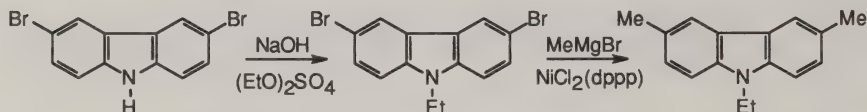
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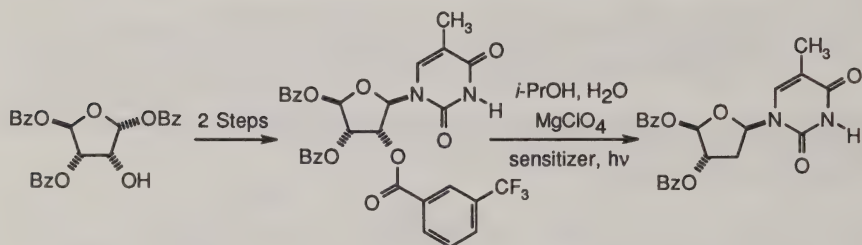
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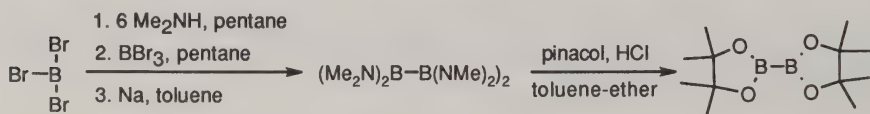
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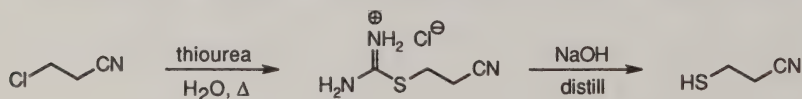
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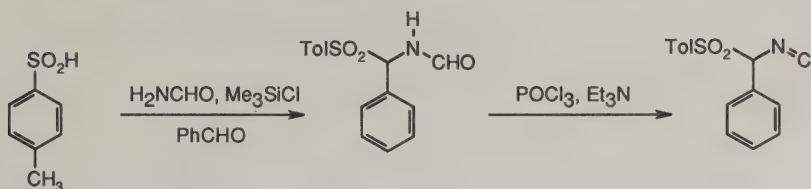
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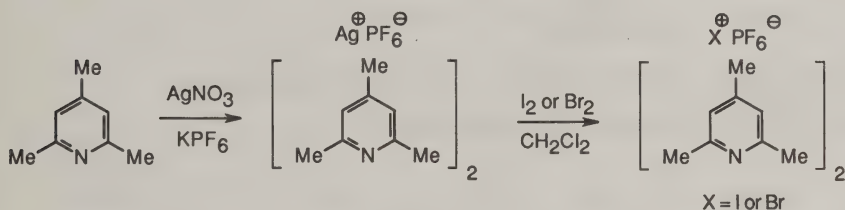
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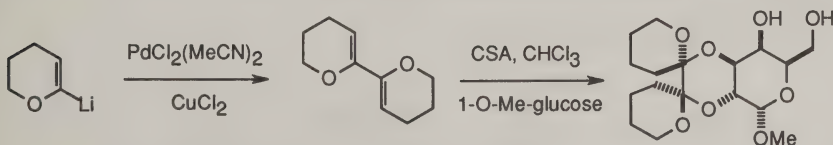
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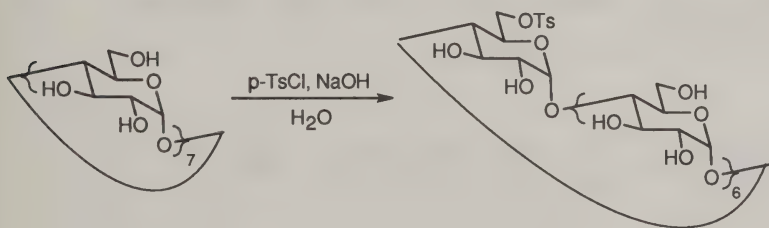
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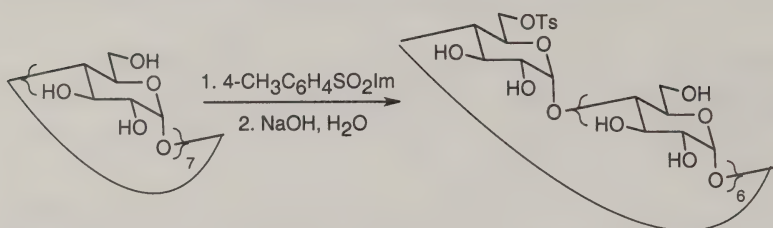
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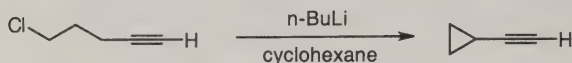
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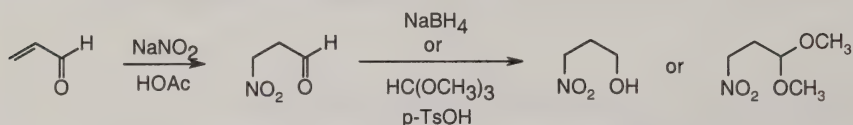
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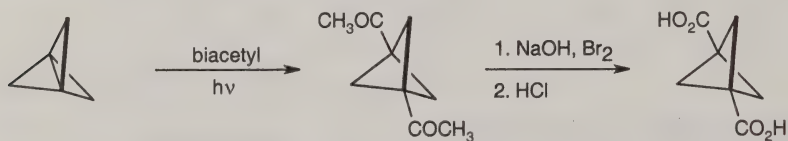
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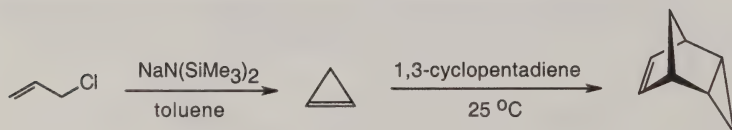
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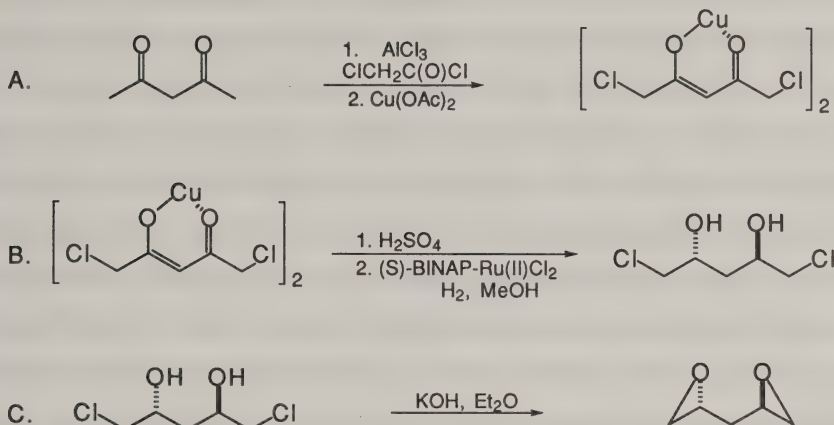
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ORGANIC SYNTHESSES

PREPARATION OF (R,R)-1,2:4,5-DIEPOXYPENTANE
(D-threo-Pentitol, 1,2:4,5-dianhydro-3-deoxy-)



Submitted by Scott D. Rychnovsky, George Griesgraber, and Jay P. Powers.¹

Checked by Gavin F. Painter and Andrew B. Holmes.

1. Procedure

Caution! Part A of this procedure must be carried out in a well-ventilated hood and the apparatus must be equipped with a hydrogen chloride (HCl) trap to avoid exposure to HCl gas.

Caution! The 1,2:4,5-diepoxy-pentanes are bisalkylating agents and have been identified as mutagens.² They should be considered carcinogenic and handled with care.

A. *Bis(1,5-dichloro-2,4-pentanedione)copper(II) complex.*³ A dry, 1-L, three-necked, round-bottomed flask is equipped with a 250-mL addition funnel, reflux condenser, rubber septum with nitrogen inlet, and a magnetic stirrer bar. The reflux

condenser is equipped with a line to an HCl trap (Note 1) and the apparatus is maintained under a positive flow of nitrogen. The flask is charged with aluminum chloride (65.0 g, 0.487 mol) followed by the addition of nitrobenzene (82 mL) (*Caution! Evolution of HCl gas*) via the addition funnel. 1,2-Dichloroethane (96 mL) (Note 2) is added via the addition funnel and the mixture is stirred until all solids dissolve (ca. 15 min). The resulting olive green solution is placed in an ice bath, and the funnel is charged with 2,4-pentanedione (50.0 mL, 0.487 mol) (Note 3). The 2,4-pentanedione is added to the solution dropwise over 15 min (*Caution! Evolution of HCl gas*), and the funnel is charged with chloroacetyl chloride (85.0 mL, 1.07 mol) (Note 4). The chloroacetyl chloride is added to the solution dropwise over 15 min, followed by removal of the ice bath. The dark green solution is allowed to warm for 30 min. The reflux condenser is replaced with a thermometer and the addition funnel is replaced with a jacketed short path distillation head connected to a vacuum adapter. The vacuum adapter on the distillation head is connected to the HCl trap and the flask is immersed in an electrically heated oil bath equipped with a magnetic stirrer and external thermometer (Note 5). The reaction is slowly heated over 2 hr to 60°C (Note 6) when acetyl chloride begins to distill (collected at 39°C). The solution temperature is maintained between 60°C and 70°C for the course of the distillation (Note 7). When the distillate temperature falls below 35°C the oil bath is removed, and the solution is cooled to room temperature with an ice bath. The solution is poured into a 2-L Erlenmeyer flask containing 1 L of ice, concentrated hydrochloric acid (80 mL), and a magnetic stirrer bar. The reaction flask is rinsed with 1 N HCl (3 x 50 mL), and the washings are added to the Erlenmeyer flask. The rust colored reaction mixture is stirred vigorously for 17 hr and the phases are separated. The aqueous phase is extracted with diethyl ether (2 x 150 mL) and the organic layers are combined. The organic layers are added to 1 L of a saturated copper(II) acetate solution in a 2-L Erlenmeyer flask, and the resulting green-brown suspension is stirred vigorously with

a magnetic stirrer for 3 hr. The solution is filtered through a Buchner funnel, and the green solid is washed with diethyl ether (3 x 100 mL). The solid is triturated with 125 mL of diethyl ether, refiltered, and washed with diethyl ether (5 x 75 mL) to give 55.6-56.4 g of product as a green-gray powder (57-58% based on 2,4-pentanedione) (Note 8).

B. (2R,4R)-1,5-Dichloro-2,4-pentanediol. Catalyst preparation: A 100-mL Schlenk flask is equipped with a magnetic stirrer bar, rubber septum, and an argon vacuum line. The flask is flame-dried under vacuum and cooled under oxygen-free dry argon (twice), and it is then charged with 1,5-cyclooctadieneruthenium(II) chloride (RuCl_2 , COD) (79.2 mg, 0.283 mmol) (Note 9) and [(S)-BINAP, 212 mg, 0.340 mmol] (Note 10). The flask and its contents are purged by evacuation and flushed with argon (twice). Triethylamine (Et_3N , 470 μL , 3.37 mmol) (Note 11) is added via syringe followed by toluene (20 mL) via cannula. The solution is heated at reflux for 16 hr under argon, then allowed to cool to room temperature. The resulting orange solution is concentrated by stirring while the flask is held at a vacuum of ca. 1 mm and the toluene and excess triethylamine are condensed in a liquid nitrogen trap to give crude $[\text{RuCl}_2\text{-(S)-BINAP}]_2\text{-Et}_3\text{N}$ catalyst as an orange solid.

1,5-Dichloro-2,4-pentanedione. A 1-L, round-bottomed flask is charged with bis(1,5-dichloro-2,4-pentanedione)copper(II) complex (22.0 g, 55.1 mmol) followed by diethyl ether (200 mL) and 10% sulfuric acid (200 mL). The reaction is stirred vigorously until all the solid dissolves (ca. 45 min). The organic layer is separated and the aqueous phase is extracted with ether (2 x 200 mL). The combined ether layers are washed with brine (2 x 300 mL) and dried (Na_2SO_4). The drying agent is removed by filtration, and the ether phase is concentrated under reduced pressure. The resulting crude material (ca. 20 g) is hydrogenated without further purification (Note 12).

The crude dione (ca. 20 g) is dissolved in dry methanol (MeOH, 40 mL) (Note 13), and the solution is degassed with a stream of dry oxygen-free argon. This solution is transferred via cannula into the flask containing the freshly prepared [RuCl₂-(S)-BINAP]-Et₃N catalyst under argon. The resulting suspension is stirred and heated with a hair dryer to dissolve the catalyst. The resulting solution is transferred via cannula under argon pressure into a flame-dried, 250-mL Schlenk flask sealed with a septum and vented with a syringe needle. The septum is replaced with a high-vacuum stopcock (Note 14) and the Schlenk flask is transferred to a nitrogen glove box where the contents are transferred to a 250-mL pressure reaction vessel equipped with a magnetic stirring bar. The vessel is sealed (Note 15). The pressure vessel is then transferred from the glove box to an electrical heating jacket preheated to 70°C and the vessel is pressurized to 1250 psi with hydrogen gas in an explosion proof fume hood. The vessel is heated until the internal temperature is 65°C, and the contents are stirred with a magnetic stirrer at that temperature for 12-14 hr (Note 16). The vessel is cooled to room temperature and cautiously vented to discharge excess hydrogen gas. The reaction mixture is concentrated under reduced pressure and filtered through a plug of silica gel that is washed with 1:1 ethyl acetate/hexanes (ca. 300 mL). Solvent is removed on a rotary evaporator and the crude product is crystallized from a mixture of hexane:dichloromethane (2:3, v/v), and the solid is collected by suction filtration and rinsed with a mixture of hexane:CH₂Cl₂ (2:3, v/v). The off-white solid is recrystallized from hexane:CH₂Cl₂ (2:3, v/v), to give three crops of crystals (Note 17). The combined yield of the white crystalline product is 7.66 g (40%) (Note 18).

C. *(2R,4R)*-1,2:4,5-Diepoxy*pentane*. A 1-L, round-bottomed flask with a magnetic stirrer bar is charged with *(2R,4R)*-1,5-dichloro-2,4-pentanediol (6.00 g, 34.7 mmol) and diethyl ether (270 mL), and the solution is cooled to 0°C. Freshly powdered potassium hydroxide (KOH, 18.5 g, 330 mmol) is added and the solution is

stirred for 3 hr at 25°C (Note 19). The reaction mixture is filtered through a plug of magnesium sulfate (MgSO_4), and the ether is removed under reduced pressure from an ice bath to give 3.20 g (92%) of the product as a colorless oil (Note 20). The optical purity of the product is >97% ee (Note 21).

2. Notes

1. The reflux condenser is fitted with an outlet that is connected with Tygon tubing to a Drechsel bottle and then an inverted funnel in a crystallizing dish filled with water which serves as the HCl trap (the submitters used Lab Glass #LG-8605).

2. 1,2-Dichloroethane, 99%, was purchased from Aldrich Chemical Company, Inc., and used without further purification.

3. 2,4-Pentanedione, 99+%, was purchased from Aldrich Chemical Company, Inc., and used without further purification.

4. Chloroacetyl chloride, 98%, was purchased from Aldrich Chemical Company, Inc., and used without further purification.

5. The submitters heated the flask with a heating mantle and wrapped the exposed part of the flask in glass wool. This serves as an insulator to allow the subsequent distillation to proceed at lower temperatures.

6. Care must be taken not to heat the reaction mixture above 70°C.

7. The distillation typically requires 8-10 hr. Note that there is a slow nitrogen stream running *through* the apparatus when set up as described. The checkers found that the acetyl chloride only condensed when the nitrogen flow was decreased or stopped.

8. The submitters obtained 58.6 g (60%) of a gray powder.

9. 1,5-Cyclooctadieneruthenium(II) chloride, 95%, was purchased from Aldrich Chemical Company, Inc., and used without further purification.

10. (S)-(-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, 99% was purchased from Aldrich Chemical Company, Inc., and used without further purification.

11. Triethylamine was distilled from calcium hydride and stored over KOH under argon. Toluene was distilled from and stored over sodium under argon.

12. The crude dione could be purified at this stage by Kugelrohr distillation (oven temp. 80°C at 1 mm) to give the 1,5-dichloro-2,4-pentanedione as a clear, colorless oil. The enol:keto ratio is ca. 5.7:1. The physical properties are as follows: ¹H NMR (250 MHz, CDCl₃) (enol) δ: 4.07 (s, 4 H), 6.14 (bs, 1 H), the acidic OH was not recorded; ¹³C NMR (62.5 MHz, CDCl₃) (enol) δ: 44.1, 96.8, 187.3; ¹H NMR (250 MHz, CDCl₃) (keto) δ: 3.95 (bs, 2 H), 4.16 (s, 4 H); ¹³C NMR (62.5 MHz, CDCl₃) (keto) δ: 48.3, 50.5, 196.2.

13. The checkers used MeOH that had been freshly distilled from sodium methoxide (NaOMe) that was stored over 3 Å molecular sieves under argon. The submitters used Fisher ACS certified methanol without purification.

14. A J. Young high vacuum stopcock was purchased from Aldrich Chemical Company, Inc.

15. A Bergof 250-mL autoclave with PTFE seal was used. The submitters did not use a glove box. They used a Parr #4751, 125-mL pressure vessel that was assembled with a glass liner and a magnetic stirring bar, but without the top fitting. They then purged the vessel with a stream of Ar, and then the reaction mixture was added from the Schlenk flask via cannula through the top opening of the pressure vessel. The valve block assembly was attached, and hydrogenation was begun. The reaction vessel was wrapped in heating tape or placed in a heating mantle and pressurized to 1250 psi with H₂ gas in an explosion proof fume hood.

16. Temperature control is important for the success of the reaction. The internal temperature should be monitored, and the temperature should be held around 65°C. The submitters found that when the autoclave (Parr #4751) is heated with heating tape

and the internal temperature cannot be monitored, an externally measured temperature of ca. 100°C is appropriate. Too high a temperature leads to cyclization of the diol to give 2-chloromethyl-4-hydroxytetrahydrofuran.

17. The second crop of crystals was obtained by concentrating the supernatant from the first crystallization under reduced pressure, then redissolving in a minimum hexane:CH₂Cl₂ (2:3, v/v). The third crop was obtained in a similar manner.

18. The submitters obtained 7.40 g (39%). The physical properties are as follows: mp 85-86°C; $[\alpha]_D^{24} +21.1$ (CHCl₃, c 1.125); IR (KBr) cm⁻¹: 3364, 2959, 2890, 1435, 1402, 1340, 1294, 1103, 1072, 1052, 910, 710; ¹H NMR (250 MHz, acetone-d₆) δ: 1.70 (dd, 2 H, J = 6.9, 5.4), 3.50-3.65 (m, 4 H), 4.02-4.12 (m, 2 H), 4.22 (d, 2 H, J = 5.6); ¹³C NMR (62.5 MHz, acetone-d₆, APT) δ: 38.7, 50.8, 68.0. Anal. Calcd. for C₅H₁₀Cl₂O₂: C, 34.71; H, 5.83. Found C, 34.7; H, 5.8. The optical purity of the 1,5-dichloro-2,4-pentanediol can be assayed by its Mosher ester analysis. The checkers prepared the bis-Mosher ester from the (R,R)-diol with (R)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride acid chloride as follows: A flame-dried flask, under argon, is charged with (2R,4R)-1,5-dichloro-2,4-pentanediol (10 mg, 0.058 mmol) and 4-dimethylaminopyridine (DMAP) (ca. 1 mg). The flask is evacuated, then repressurized with argon. Following the addition of dry Et₃N (55 μL, 0.39 mmol) (Note 11) and dry CH₂Cl₂ (3 mL) (dried over calcium hydride and stored over 4 Å molecular sieves), (R)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Aldrich Chemical Company, Inc.) (50 mg, 0.20 mmol) is added, and the reaction mixture is stirred at 25°C under argon for 24 hr, at which time silica TLC (silica gel, 50% EtOAc/hexane) indicated that no diol remained. The reaction mixture is concentrated under reduced pressure and filtered through a plug of silica (CH₂Cl₂) to give the bis Mosher ester (25 mg, 0.041 mmol, 71%); $[\alpha]_D^{22} +50.0$ (CHCl₃, c 0.30); ¹H NMR (500 MHz, CDCl₃) δ: 2.20 (dd, 2 H, J = 7.3, 5.7 (central CH₂)), 3.53 (bs, 6 H, OMe), 3.57 (dd, 2 H, J = 12.1, 4.0), 3.69 (dd, 2 H, J = 12.0, 4.9), 5.13-5.21 (m, 2 H), 7.41-7.45 (m, 6 H), 7.50-7.55 (m,

4 H); ^{19}F NMR (235 MHz, CDCl_3) δ : -69.6; FAB-MS m/z 627.0785 ($[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{25}\text{H}_{24}\text{Cl}_2\text{F}_6\text{O}_6\text{Na}$ 627.0752), 605 (5), $[\text{M}]^+$, 535 (5), 472 (3), 371 (5), 189 (100). The diastereomeric bis Mosher ester derived from the (S,S)-diol and (R)-acid chloride displays the central CH_2 as a doublet of doublets ($J = 7.5, 5.5$) at δ 2.07.

19. The KOH is ground with a mortar and pestle in a fume hood, and the ether is used as supplied. The submitters noted that when very dry KOH and ether were used, the reaction did not proceed to completion. They then effected the reaction with 50% aqueous KOH solution instead of powdered KOH, followed by a standard aqueous workup.

20. The submitters obtained 4.50 g (45.0 mmol, 90%) from 8.65 g (50 mmol) of diol. A sample purified by Kugelrohr distillation (bp 65°C at 28 Torr) gave the following spectral data: $[\alpha]_{\text{D}}^{24} +57.6$ (CHCl_3 , c 2.24); IR (neat) cm^{-1} : 3055, 2997, 2924, 1421, 1256, 980, 938, 912, 844, 792, 747; ^1H NMR (300 MHz, CDCl_3) δ : 1.72 (t, 2 H, $J = 5.7$), 2.51 (dd, 2 H, $J = 4.9, 2.6$), 2.73 (dd, 2 H, $J = 4.9, 4.1$), 3.03-3.09 (m, 2 H); ^{13}C NMR (75 MHz, CDCl_3 , DEPT) δ : 36.2, 46.9, 49.5. Anal. Calcd. for $\text{C}_5\text{H}_8\text{O}_2$; C, 59.98; H, 8.05. Found C, 60.0; H, 8.2.

21. The enantiomeric purity of the (R,R)-1,2:4,5-diepoxy pentane was measured as 96% by comparing the sample with (S,S)-1,2:4,5-diepoxy pentane using GC analysis on a B-PH (beta-cyclodextrin, permethylated hydroxypropyl) GC column. The submitters prepared both (S,S)- and (R,R)-enantiomers with enantiomeric excess >97% using the enantiomeric BINAP-Ru(II) Cl_2 catalysts. The enantiomeric purity of their 1,2:4,5-diepoxy pentane was assayed by GC analysis using a B-PH (β -cyclodextrin, permethylated hydroxypropyl) column (20 m x 0.25 mm x 0.25 μm); split ratio = 100:1; column flow 1.0 mL/min.; 50°C - 5 min; $3^\circ\text{C}/\text{min}$ until 150°C . Retention times: (R,R)-12.55 min; (S,S)-12.75 min.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The (R,R)-1,2:4,5-diepoxy-pentane was first prepared in optically pure form by Ley using a multistep route from D-(+)-ribonic acid γ -lactone.^{4b} Ley used this diepoxide as a linchpin to assemble the spiroacetal segments of (+)-milbemycin β_1 ⁴ and avermectin B_{1a}.⁵ The route described here⁶ is based on the enantioselective hydrogenation of 1,5-dichloro-2,4-pentanedione³ using Ru(BINAP)Cl₂ catalyst.⁷ Both the (R,R)- and the (S,S)-1,2:4,5-diepoxy-pentane can be prepared by this route using the appropriate BINAP catalyst. The C₂ symmetric diepoxy-pentanes are very useful synthons for anti-1,3-diols⁶ and have been key precursors in the synthesis of roflamycoin and its isomer.⁸ They also have been used to prepare optically pure A-ring intermediates for the synthesis of vitamin-D₃ analogs.⁹

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(R,R)-1,2:4,5-Diepoxy-pentane: D-threo-Pentitol, 1,2:4,5-dianhydro-3-deoxy-(12)- (109905-51-3)

Bis(1,5-dichloro-2,4-pentanedione) copper(II) complex: Copper, bis(1,5-dichloro-2,4-pentanedionato-O,O')- (12); (135943-96-3)

Aluminum chloride (8,9); (7446-70-0)

Nitrobenzene: HIGHLY TOXIC: Benzene, nitro- (8,9); (98-95-3)

2,4-Pentanedione (8,9); (123-54-6)

Chloroacetyl chloride: Acetyl chloride, chloro- (8,9); (79-04-9)

(2R,4R)-1,5-Dichloro-2,4-pentanediol: 2,4-Pentanediol, 1,5-dichloro-, [R-(R*,R*)]- (12); (136030-28-9)

1,5-Cyclooctadieneruthenium(II) chloride: Ruthenium, dichloro[(1,2,5,6-η)-1,5-cyclooctadiene]- (9); (50982-12-2)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

(S)-(-)-BINAP: (S)-(-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl: Phosphine, [1,1'-binaphthalene]-2,2'-diylbis(diphenyl-, (S)- (10); (76189-56-5)

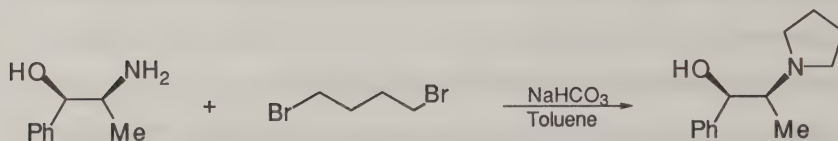
Ruthenium chloride-(S)-BINAP-triethylamine: Ruthenium, bis[[1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine]-P,P']di-μ-chlorodichloro(N,N-diethylethanamine)di- (12); (114717-51-0)

1,5-Dichloro-2,4-pentanedione: 2,4-Pentanedione, 1,5-dichloro- (9); (40630-12-4)

Hydrogen (8,9); (1333-74-0)

Potassium hydroxide (8,9); (1310-58-3)

**PREPARATION OF [R-(R*,S*)]-β-METHYL-α-PHENYL-
1-PYRROLIDINEETHANOL**
(1-Pyrrolidineethanol, β-methyl-α-phenyl-, [R-(R*,S*)]-)



Submitted by Dalian Zhao, Cheng-yi Chen, Feng Xu, Lushi Tan, Richard Tillyer,^{1a}
Michael E. Pierce, and James R. Moore.^{1b}

Checked by Jonathan W. Burton and Andrew B. Holmes.

1. Procedure

A 500-mL, three-necked, round-bottomed flask, equipped with a mechanical stirrer, condenser with Dean-Stark trap, nitrogen bubbler and a thermometer (Note 1), is charged with toluene (200 mL), (1R,2S)-(-)-norephedrine (37.8 g, 0.25 mol), 1,4-dibromobutane (59.38 g, 0.275 mol) and sodium bicarbonate (46.2 g, 0.55 mol) (Note 2). The stirred heterogeneous reaction mixture is heated to reflux (105-118°C, Note 3) under a nitrogen atmosphere until completion of the reaction (Note 4). At the end of the reaction approximately 9 mL of water has collected in the Dean-Stark trap (Note 5).

The reaction mixture is cooled to ambient temperature, filtered through a sintered glass funnel to remove inorganic salts, and the cake is washed with toluene (75 mL). The combined filtrate and wash are washed with water (150 mL). The organic layer is separated, and placed in a 500-mL, three-necked flask equipped with a mechanical stirrer. The toluene solution is concentrated by reduced pressure distillation with mechanical stirring (45-50°C, 25-30 mm) to a volume of approximately

120 mL, and the final volume is adjusted to approximately 250 mL with toluene (Note 6).

The toluene solution is cooled to 10-15°C and hydrochloric acid (HCl) in 2-propanol (0.275 mol) (Note 7) is added slowly over 1 hr via a pressure-equalizing dropping funnel, keeping the internal temperature below 25°C (Note 8). During the acid addition the product precipitates as its hydrochloride salt. The mixture is stirred at room temperature under nitrogen for 2 hr, and is reduced in volume by distillation under reduced pressure (45-50°C, 25-30 mm) with mechanical stirring to produce a distillate of approximately 120 mL and a residual volume of about 100 mL. Toluene (50 mL) is added and the slurry is reconcentrated under reduced pressure (45-50°C, 25-30 mm) until a residual volume of 100 mL is obtained. This process is repeated once more (Note 9). Toluene is added to adjust the total volume to about 250 mL. The mixture is then cooled to 10-15°C and stirred under nitrogen at this temperature for 2 hr. The HCl salt is isolated by filtration and the wet cake is washed with toluene (2 x 50 mL).

The wet cake (Note 10) is transferred to a mixture of 100 mL of heptane and 138 mL of 2 M sodium hydroxide (NaOH) with stirring (Note 11). The two layers are separated. The aqueous layer (pH > 12) is extracted with heptane (75 mL). The combined organic layers are washed with water (50 mL), filtered through a cotton wool plug and concentrated under reduced pressure (rotary evaporator, ca. 30 mm). The residue is transferred to a three-necked flask equipped with a mechanical stirrer and thermometer, and the volume is adjusted to 120 mL. The mechanically stirred solution is cooled to -25°C to form a slurry. The slurry is stirred under nitrogen at -25°C for 1 hr and then filtered through a precooled (-18°C, freezer) sintered glass funnel. The solid is rapidly washed with 25 mL of heptane that is precooled (freezer) and then dried by suction to give [R-(R*,S*)]-β-methyl-α-phenyl-1-pyrrolidineethanol as an off-white crystalline solid (45.9 g, 90% yield, Notes 12 and 13).

2. Notes

1. The submitters used a thermocouple to monitor the temperature.

2. The submitters purchased (1R,2S)-(-)-norephedrine from Alps Pharmaceutical Co. and 1,4-dibromobutane from Leeds Chemical Co. For small scale reactions (50 g or less) both compounds can be purchased from the Aldrich Chemical Company, Inc.

3. Efficient mechanical stirring and gentle heating are essential to avoid bumping during the early stages of the reaction when gas evolution is at a maximum. The reaction temperature gradually increases from 105°C to 118°C as the reaction progresses.

4. The reaction typically takes 18-22 hr to complete and completion of the reaction is easily monitored by TLC (silica gel; diethyl ether saturated with aqueous ammonia; R_f of norephedrine 0.05; R_f of product 0.2). An alternative HPLC assay can also be used. HPLC sample preparation: A 50- μ L filtered clear reaction solution (Whatman syringe filter 0.45 μ M PTFE) is dissolved in acetonitrile (MeCN) to 50 mL. The ratio of the product to starting material (1R,2S)-(-)-norephedrine HPLC area percentage should be 99:1 or higher at the end of the reaction. HPLC Column (used by checkers): Rainin Dynamax® 5-mm x 25-cm C₁₈ (the submitters used 4.6-mm x 25-cm Inertsil phenyl). Eluent: MeCN / pH 6.0 phosphate buffer, 15 mM (8.28 g NaH₂PO₄·H₂O and 0.8 mL of triethylamine (Et₃N) in 4 L of HPLC grade water) (45/55 v/v) (the submitters used these solvents in a gradient elution: 15% MeCN kept for 5 min then changed to 45% MeCN over 11 min and kept at this ratio for another 6 min). Injection: 20 μ L; flow rate: 0.75 mL/min (submitters used 1.5 mL/min). Detection: 210 nm; temperature: 23°C. Retention times: norephedrine: 3.9 min; product: 6.7 min. (The submitters observed sodium bromide: 1.8 min; norephedrine: 5.0 min; product: 12.0 min; toluene: 22.5 min).

5. Water is generated soon after the reaction mixture begins to reflux and is mostly removed by the toluene-water azeotropic distillation. The presence of a small amount of water appears to be essential to the reaction. However, too much water remaining in the reaction mixture mixes with the inorganic salts and forms a sticky, wet solid lump at the bottom of the flask that could be a potential problem for the stirring and subsequent filtration.

6. Removal of most of the water in the toluene solution increases the recovery of the [R-(R*,S*)]- β -methyl- α -phenyl-1-pyrrolidineethanol HCl salt. The temperature must be kept below 50°C to avoid bumping. This step can be carried out on a rotary evaporator.

7. The HCl in 2-propanol solution (5-6 M) was purchased from Acros Organics. Titration against NaOH solution revealed a concentration of 4.8 M. The titer varies according to batches. The actual volume of HCl in 2-propanol solution was selected to deliver 1.1 mol equiv of HCl.

8. Purification by formation of the [R-(R*,S*)]- β -methyl- α -phenyl-1-pyrrolidineethanol HCl salt is necessary to remove non-amine organic components such as 1,4-dibromobutane that are known to decrease the enantioselectivity of the subsequent chiral addition reaction (Scheme 1).

9. 2-Propanol and residual amounts of water are removed by distillation to minimize the loss of the [R-(R*,S*)]- β -methyl- α -phenyl-1-pyrrolidineethanol HCl salt that is soluble in 2-propanol. The submitters monitored product concentration in the supernatant liquid using HPLC (Note 4) relative to a standard concentration of analytically pure product to ensure that the concentration was less than 3 mg/mL. While the checkers did monitor the concentration of the product in the supernatant liquid, reproducibly high yields of product were realized without carrying out the monitoring procedure.

10. The wet cake was partially dried for 12 hr in a 500-mL, round-bottomed flask at 25°C under vacuum (5 mm). The submitters partially dried the wet cake under nitrogen/vacuum for 2-3 hr and used it directly in the next salt-breaking step. They prepared a fully dried sample for storage by drying in a vacuum oven (~50 mm, 40°C for 1-2 days).

11. Alternatively, [R-(R*,S*)]-β-methyl-α-phenyl-1-pyrrolidineethanol free base may be prepared as a toluene solution. The solution could be used directly in the chiral addition reaction (Scheme 1).

12. The submitters ran the procedure on different scales (10 g to 30 kg) with yields ranging from 90-94%.

13. The product is fully characterized: mp 44-45°C. The checkers obtained $[\alpha]_D^{20} +15.7$ (CHCl₃, *c* 2.05). The submitters reported $[\alpha]_D^{20} +15.2$ (CHCl₃, *c* 2.00). The specific rotation of the enantiomer (1S,2R)-N-pyrrolidinylnorephedrine has been reported:² $[\alpha]_D^{20} -7.3$ (*c* 2, CHCl₃); IR (CDCl₃) cm⁻¹: 3440 (OH), 2970, 2805, 1450, 1380, 1200, and 975; ¹H NMR (250 MHz, CDCl₃) δ: 0.80 (d, 3 H, *J* = 6.5), 1.79-1.84 (m, 4 H), 2.47 (qd, 1 H, *J* = 6.5, 3), 2.6-2.7 (m, 2 H), 2.7-2.9 (m, 2 H), 3.69 (s, 1 H), 5.00 (d, 1 H, *J* = 3), 7.23-7.35 (m, 5 H); ¹³C NMR (62.5 MHz, CDCl₃) δ: 12.0, 23.5, 51.8, 65.3, 72.7, 125.8, 126.7, 128.0, 141.7. MS (ES⁺) *m/z* (rel intensity) 206 [100, (M + H)⁺]. Anal. Calcd. for C₁₃H₁₉NO: C, 76.1; H, 9.3; N, 6.8. Found: C, 76.3, H, 9.3; N, 6.9.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

[R-(R*,S*)]- β -Methyl- α -phenyl-1-pyrrolidineethanol is an important chiral mediator for the enantioselective addition of an acetylide to a prochiral ketone.^{2,3} This reaction has been successfully applied to the synthesis of the reverse transcriptase inhibitor efavirenz (DMP-266) (Scheme 1).^{3,4} Preparation of the enantiomer, (1S,2R)-N-pyrrolidinylnorephedrine, has been reported.² The method used potassium carbonate (K_2CO_3) as base, but the yield of the product was only 33%. The submitters have extensively studied the formation of the pyrrolidiny ring under various conditions as summarized in Table I. Eventually they found that the reaction was extremely efficient when it was run in toluene using sodium bicarbonate ($NaHCO_3$) as base (entry 8, Table I),⁵ which gave [R-(R*,S*)]- β -methyl- α -phenyl-1-pyrrolidineethanol quantitatively. Enantioselective (up to 99% ee) addition of cyclopropylacetylene to the ketoaniline **1** is achieved when the solution of [R-(R*,S*)]- β -methyl- α -phenyl-1-pyrrolidineethanol is used as a chiral additive.³ In addition, this method is also applicable to the preparation of a variety of alkylated norephedrine and other amino alcohols in excellent yields as illustrated in Table II. These amino alcohols are potentially useful in asymmetric syntheses.

1. (a) Process Research Department, Merck Research Laboratories, Division of Merck & Co., Inc., P.O. Box 2000, Rahway, NJ 07065; (b) Chemical Process R & D, DuPont Pharmaceuticals, Chambers Works, Deepwater, NJ 08023.
2. Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264; Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. I* **1990**, 937.
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5. Synthesis of pyrrolidyl alkanols using NaHCO₃ as a base was reported to give pyrrolidyl derivatives in moderate yields. Moffett, R. B. *J. Org. Chem.* **1949**, *14*, 862.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

[R-(R* S*)]-β-Methyl-α-phenyl-1-pyrrolidineethanol: 1-Pyrrolideneethanol, β-methyl-α-phenyl-, [R-(R*,S*)]- (12); (127641-25-2)

(1R, 2S)-(-)-Norephedrine: Norephedrine (8); Benzeneethanol, α-(1-aminoethyl)-, [R-(R*, S*)]- (9); (492-41-4)

1,4-Dibromobutane: Butane, 1,4-dibromo- (8,9); (110-52-1)

Hydrochloric acid in 2-propanol: Hydrochloric acid (8,9); (7647-01-0)

Scheme 1

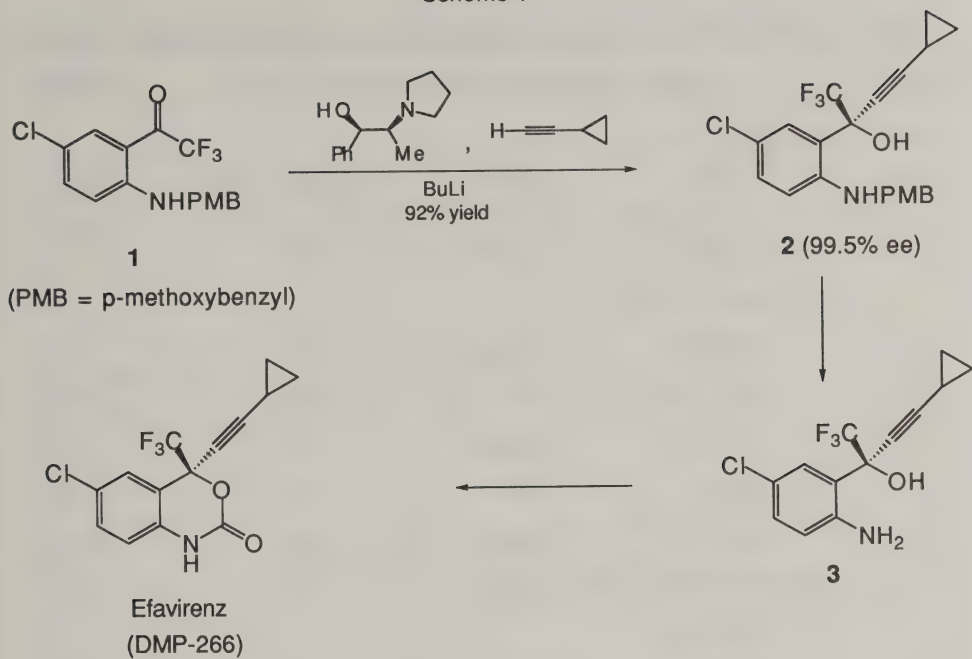
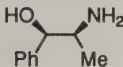
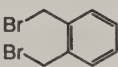
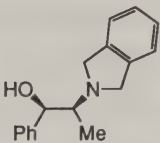
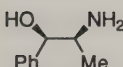
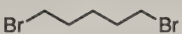
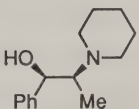
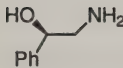

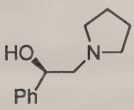
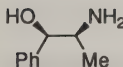
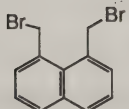
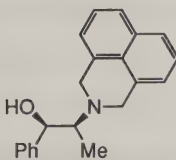
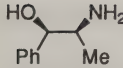

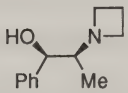
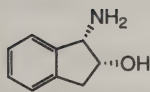

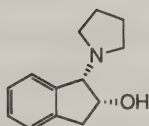
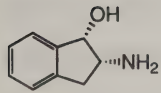

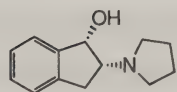


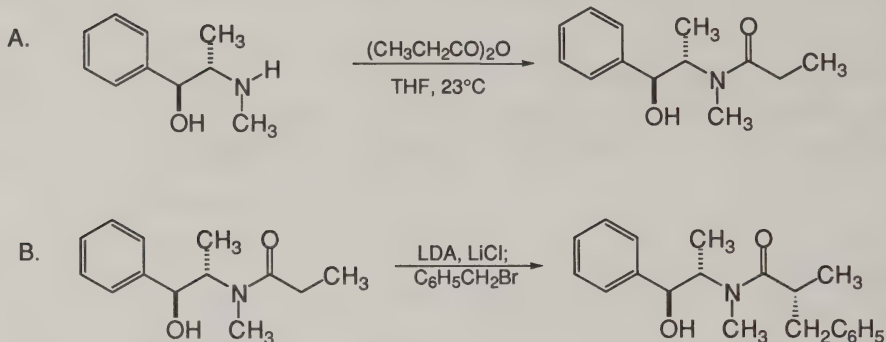
TABLE I
PREPARATION OF [R-(R*,S*)]- β -METHYL- α -PHENYL-1-PYRROLIDINEETHANOL
WITH DIFFERENT BASES AND SOLVENT

Entry	Base	Solvent	Temperature (°C)	Yield (%)
1	Aq. K ₂ CO ₃ (1:1 water: K ₂ CO ₃)	n-BuOH	95	75
2	5 N NaOH	Toluene	93	87
3	5 N NaOH	THF	65	91
4	5 N NaOH	Heptane	88	82
5	NaHCO ₃	THF	67	90
6	NaHCO ₃	Heptane	95	76
7	Na ₂ CO ₃ /NaHCO ₃ /NaI (1.0:1.0:0.5)	Toluene	110	80
8	NaHCO ₃	Toluene	115	94

TABLE II
PREPARATION OF N-ALKYLATED NOREPHEDRINE ANALOGS

Ephedrine	Alkyl Halide	Product	Yield (%)
			93
			98
			97
			81
			96
			95
			95

SYNTHESIS AND DIASTEREOSELECTIVE ALKYLATION OF PSEUDOEPHEDRINE AMIDES



Submitted by Andrew G. Myers and Bryant H. Yang.¹

Checked by William J. Smith, III and William R. Roush.

1. Procedure

A. *(1S,2S)*-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methylpropionamide, (*(1S,2S)*-pseudoephedrinepropionamide). A flame-dried, 1-L, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with 21.3 g (129 mmol) of (*(1S,2S)*)-(+)-pseudoephedrine (Note 1) and 250 mL of tetrahydrofuran (Note 2). The flask is placed in a water bath at 23°C, and to the well-stirred solution, 18.0 g (138 mmol) of propionic anhydride (Note 3) is added by a Pasteur pipette in 1-mL portions over approximately 5 min. The flask is sealed with a rubber septum containing a needle adapter to an argon-filled balloon, and the clear, colorless solution is allowed to stir at 23°C for an additional 10 min. The rubber septum is removed, and the reaction solution is neutralized by the addition of 400 mL of saturated aqueous sodium bicarbonate solution. After thorough mixing (Note 4), the biphasic mixture is poured

into a separatory funnel and extracted with three portions of ethyl acetate (250 mL, 150 mL, and 150 mL, respectively). The combined organic extracts are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford a white solid. Residual solvent is removed under vacuum (0.5 mm) for 3 hr. The solid residue is dissolved in 125 mL of hot (110°C) toluene in a 250-mL Erlenmeyer flask, and the flask is placed in a water bath at 80°C. This bath is allowed to cool slowly to 23°C. Extensive crystallization occurs as the solution cools. Crystallization is completed by cooling the flask to -20°C. After 10 hr, the crystals are collected by filtration and rinsed with 100 mL of cold (0°C) toluene. The crystals are dried under reduced pressure (0.5 mm) at 23°C for 3 hr to afford 27.2 g (95%) of the (1S,2S)-pseudoephedrinepropionamide as a white solid (Note 5).

B. [1S(R),2S]-N-(2-Hydroxy-1-methyl-2-phenylethyl)-N,2-dimethylbenzene-propionamide, [(1S,2S)-pseudoephedrine-(R)-2-methylhydrocinnamamide]. A flame-dried, 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and an inlet adapter connected to a source of argon is charged with 25.0 g (590 mmol) of anhydrous lithium chloride (Note 6) and sealed with a rubber septum. The inlet adapter is removed and replaced with a rubber septum containing a needle adapter to an argon-filled balloon. The reaction flask is charged with 31.3 mL (223 mmol) of diisopropylamine (Note 7) and 120 mL of tetrahydrofuran (Note 2). The mixture is cooled to -78°C in a dry ice-acetone bath, and 85.1 mL (207 mmol) of a 2.43 M solution of butyllithium in hexanes (Note 8) is added via cannula over 10 min. The resulting suspension is warmed to 0°C in an ice-water bath and is held at that temperature for 5 min, then cooled to -78°C. An ice-cooled solution of 22.0 g (99.4 mmol) of (1S,2S)-pseudoephedrinepropionamide in 300 mL of tetrahydrofuran (Note 2) is transferred to the cold reaction mixture by cannula over 10 min. The reaction mixture is stirred at -78°C for 1 hr, at 0°C for 15 min, at 23°C for 5 min, and finally is cooled to 0°C, whereupon 17.7 mL (149 mmol) of benzyl bromide (Note 9) is added

over 3 min via syringe. After 15 min, 5 mL of saturated aqueous ammonium chloride solution is added, and the reaction mixture is poured into a 2-L separatory funnel containing 800 mL of saturated aqueous ammonium chloride solution and 500 mL of ethyl acetate. The aqueous layer is separated and extracted further with two 150-mL portions of ethyl acetate. The combined organic extracts are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford a yellow solid. Residual solvent is removed under vacuum (0.5 mm) for 3 hr. The solid residue is dissolved in 100 mL of hot (110°C) toluene in a 250-mL Erlenmeyer flask, and the flask is placed in a water bath at 80°C. The bath is allowed to cool slowly to 23°C. Extensive crystallization occurs as the solution cools. Crystallization is completed by cooling the flask to -20°C. After 10 hr, the crystals are collected by filtration and are rinsed with 100 mL of cold (0°C) toluene. The crystals are dried under reduced pressure (0.5 mm) at 23°C for 3 hr to afford 27.8 g (90%) of the desired (1S,2S)-pseudoephedrine-(R)-2-methylhydrocinnamamide as a white solid (Note 10). The diastereomeric excess (de) of this product is determined to be $\geq 99\%$ (Note 11).

2. Notes

1. (1S,2S)-(+)-Pseudoephedrine was obtained from Aldrich Chemical Company, Inc., and was used without further purification.
2. Tetrahydrofuran was distilled from sodium benzophenone ketyl under an atmosphere of nitrogen.
3. Propionic anhydride was obtained from Aldrich Chemical Company, Inc., and used without further purification.
4. Because of the large volume of CO₂ released during the neutralization of propionic acid, care should be taken that the propionic acid is quenched before the reaction mixture is sealed and shaken inside a separatory funnel.

5. The product exhibits the following properties: mp 114-115°C; ^1H NMR (300 MHz, C_6D_6) δ : 0.53 (d, $J = 6.7$), 0.9-1.1 (m), 1.22 (t, $J = 7.3$), 1.73 (m), 2.06 (s), 2.40 (m), 2.77 (s), 3.6-3.75 (m), 4.0-4.2 (m), 4.51 (t, $J = 7.2$), 4.83 (br), 6.95-7.45 (m); ^{13}C NMR (75 MHz, CDCl_3) δ : 9.0, 9.4, 14.2, 15.2, 26.6, 27.3, 27.6, 32.1, 57.7, 58.1, 75.0, 76.1, 126.3, 126.7, 127.4, 127.9, 128.1, 128.3, 141.5, 142.2, 174.8, 175.8 (The ^1H and ^{13}C NMR spectra are complex due to amide geometrical isomerism); IR (neat) cm^{-1} : 3380 (OH), 2979, 1621 (C=O), 1454, 1402, 1053, 702; HRMS (FAB) m/z 222.1490 $[(\text{M}+\text{H})^+ \text{ calcd. for } \text{C}_{13}\text{H}_{20}\text{NO}_2: 222.1495]$. Anal. Calcd. for $\text{C}_{13}\text{H}_{19}\text{NO}_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.55; H, 8.50; N, 6.35.

6. Anhydrous lithium chloride (99+%, A.C.S. reagent grade) was purchased from Aldrich Chemical Company, Inc., and was further dried as follows. The solid reagent is transferred to a flask fitted with a vacuum adapter. The flask is evacuated (0.5 mm) and immersed in an oil bath at 150°C. After heating for 12 hr at 150°C, the flask is allowed to cool to 23°C and is flushed with argon for storage.

7. Diisopropylamine was distilled from calcium hydride under an atmosphere of nitrogen.

8. Butyllithium (2.5 M solution in hexanes) was purchased from Aldrich Chemical Company, Inc., and was titrated against diphenylacetic acid.²

9. Benzyl bromide was obtained from Aldrich Chemical Company, Inc., and purified by passage through 5 g of activated basic aluminum oxide.

10. The product exhibits the following properties: mp 136-137°C; ^1H NMR (300 MHz, C_6D_6) δ : 0.59 (d, $J = 6.8$), 0.83 (d, $J = 7.0$), 1.02 (d, $J = 6.5$), 1.05 (d, $J = 7.0$), 2.08 (s), 2.45-2.59 (m), 2.70 (s), 2.75 (m), 3.01 (m), 3.36 (dd, $J = 13.1, 6.92$), 3.80 (m), 3.96 (m), 4.25 (br), 4.45 (m), 6.9-7.4 (m); ^{13}C NMR (75 MHz, CDCl_3) δ : 14.3, 15.5, 17.4, 17.7, 27.1, 32.3, 38.1, 38.9, 40.0, 40.3, 58.0, 75.2, 76.4, 126.2, 126.4, 126.8, 127.5, 128.26, 128.31, 128.6, 128.9, 129.2, 139.9, 140.5, 141.1, 142.3, 177.2, 178.2 (The ^1H and ^{13}C NMR spectra are complex due to amide geometrical isomerism); IR (neat)

cm⁻¹: 3384 (OH), 3027, 2973, 2932, 1617 (C=O), 1493, 1453, 1409, 1080, 1050, 701;
HRMS (FAB) *m/z* 312.1972 [(M+H)⁺ calcd. for C₂₀H₂₆NO₂: 312.1965]. Anal. Calcd. for C₂₀H₂₅NO₂: C, 77.14, H, 8.09, N, 4.50. Found: C, 76.87, H, 8.06, N, 4.50.

11. The diastereomeric excess (de) of the product was determined as follows. A 10-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with 30 mg (0.096 mmol) of (S,S)-pseudoephedrine-(R)-2-methylhydrocinnamamide and 1.0 mL of dichloromethane. To the clear, colorless solution is added 49 μ L (0.35 mmol) of triethylamine and 34 μ L (0.27 mmol) of chlorotrimethylsilane. After 10 min, the cloudy reaction mixture is quenched with 5 mL of water, and the mixture is transferred to a 125-mL separatory funnel with 50 mL of 50% ethyl acetate-hexanes. The organic layer is separated and extracted further with 5 mL of water followed by 5 mL of brine. The organic layer is dried over anhydrous sodium sulfate, filtered, and concentrated. The oily residue is dissolved in ethyl acetate for capillary gas chromatographic analysis. The analysis is carried out using a Chirasil-Val capillary column (25 m x 0.25 mm x 0.16 μ m, Alltech, Inc.) under the following conditions: oven temp. 200°C, injector temp. 250°C, detector temp. 275°C. The following retention times were observed: 8.60 min (minor diastereomer), 9.27 min (major diastereomer). It should be noted that the retention times can vary greatly depending on the age and condition of the column. Dichloromethane was purchased from EM Science and was distilled from calcium hydride under an atmosphere of nitrogen. Triethylamine and chlorotrimethylsilane were purchased from Aldrich Chemical Company, Inc., and were distilled from calcium hydride under an atmosphere of nitrogen.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This procedure describes the use of pseudoephedrine as a chiral auxiliary for the asymmetric alkylation of carboxylic acid amides. In addition to the low cost and availability in bulk of both enantiomeric forms of the chiral auxiliary, pseudoephedrine, a particular advantage of the method is the facility with which the pseudoephedrine amides are formed. In the case of carboxylic acid anhydrides, the acylation reaction occurs rapidly upon mixing with pseudoephedrine. Because pseudoephedrine amides are frequently crystalline materials, the acylation products are often isolated directly by crystallization, as illustrated in the procedure above.

Pseudoephedrine amides undergo highly diastereoselective and efficient alkylation reactions. Like the alkylation substrates, the alkylation products are frequently crystalline compounds, and can often be isolated in $\geq 99\%$ de by direct crystallization from the crude reaction mixture. The procedure described above is representative of this methodology and can be generally employed with a wide range of pseudoephedrine amides and alkylating agents.^{3,4} The transformation of the alkylation products into highly enantiomerically enriched alcohols, aldehydes, and ketones, provides access to a large number of useful intermediates for organic synthesis, as described in the accompanying procedure.

1. Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125.
2. Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.
3. Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361.
4. Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(1S,2S)-N-(2-Hydroxy-1-methyl-2-phenylethyl)-N-methylpropionamide:
 Propanamide, N-(2-hydroxy-1-methyl-2-phenylethyl)-N-methyl-, [R-(R*,R*)]- (14);
 (192060-67-6); [S-(R*,R*)]- (13); (159213-03-3)

(1S,2S)-(+)-Pseudoephedrine: Pseudoephedrine, (+)- (8); Benzenemethanol,
 α -[1-(methylamino)ethyl]-, (R*,S*)-(\pm)- (9); (90-82-4)

Propionic anhydride (8); Propanoic acid, anhydride (9); (123-62-6)

[1S(R),2S]-N-(2-Hydroxy-1-methyl-2-phenylethyl)-N, 2-dimethylbenzene-
 propionamide: (1S,2S)-Pseudoephedrine-(R)-2-methylhydrocinnamide:
 Benzenepropanamide, N-(2-hydroxy-1-methyl-2-phenylethyl)-N, α -dimethyl-,
 [1S-[1R*(R*),2R*]]- (13); (159345-08-1); [1S-[1R*(S*),2R*]]- (13); (159345-06-9)

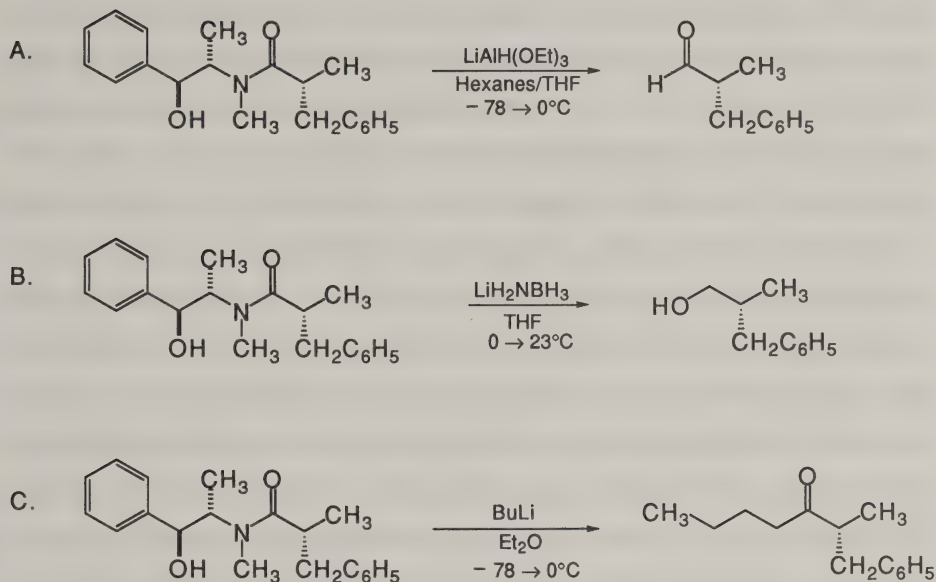
Lithium chloride (8,9); (7447-41-8)

Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Benzyl bromide: Toluene, α -bromo- (8); Benzene, (bromomethyl)- (9); (100-39-0)

**TRANSFORMATION OF PSEUDOEPHEDRINE AMIDES INTO
HIGHLY ENANTIOMERICALLY ENRICHED
ALDEHYDES, ALCOHOLS, AND KETONES**



Submitted by Andrew G. Myers, Bryant H. Yang, and Hou Chen.¹

Checked by William J. Smith, III and William R. Roush.

1. Procedure

A. *(R)*- α -Methylbenzenepropanal. A flame-dried, 1-L, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with 2.95 g (73.9 mmol) of 95% lithium aluminum hydride (Note 1) under a nitrogen atmosphere. The flask is sealed with a rubber septum containing a needle adapter to an argon-filled balloon and is charged with 170 mL of hexanes (Note 2). The septum is removed and

the flask is equipped with an oven-dried, 25-mL, pressure-equalizing addition funnel sealed with a rubber septum containing a needle adapter to an argon-filled balloon. The reaction flask is cooled to 0°C in an ice-water bath, the addition funnel is charged with 10.7 mL (109 mmol) of ethyl acetate (Note 3), and slow, dropwise addition of ethyl acetate is initiated and completed within 1.25 hr (Note 4). Upon completion of the addition, the addition funnel is removed, the reaction vessel is sealed with a rubber septum containing a needle adapter to an argon-filled balloon, and the reaction flask is cooled to -78°C in a dry ice-acetone bath. A solution of 10.0 g (32.1 mmol) of (1S,2S)-pseudoephedrine-(R)-2-methylhydrocinnamamide (Note 5) in 110 mL of tetrahydrofuran (Note 6) is added to the cold suspension of lithium triethoxyaluminum hydride² [LiAlH(OEt)₃] via cannula over 5 min. Upon completion of the addition, the dry ice-acetone bath is removed and the reaction mixture is warmed to 0°C in an ice-water bath. During the course of warming, substantial gas evolution is observed and vented using a needle as necessary. The reaction mixture is stirred at 0°C for 1 hr, then transferred via a wide-bore cannula into a vigorously stirring solution of 400 mL of 1 N aqueous hydrochloric acid solution and 25 mL (325 mmol) of trifluoroacetic acid (Note 7) in an argon-purged, three-necked, 2-L, round-bottomed flask equipped with a mechanical stirrer and two rubber septa on the side-arms, one containing a needle adapter to an argon-filled balloon. A quantitative transfer is effected with 10 mL of tetrahydrofuran, and the biphasic hydrolysis mixture is stirred vigorously for 5 min at 23°C, then is poured into a 2-L separatory funnel containing 700 mL of 1 N aqueous hydrochloric acid solution (Note 8). After the layers are shaken vigorously, they are separated and the aqueous layer is further extracted with three 150-mL portions of ethyl acetate. The combined organic layers are extracted with 250 mL of saturated aqueous sodium bicarbonate solution with care to avoid excessive build-up of pressure in the separatory funnel. The aqueous phase is separated and extracted with 100 mL of ethyl acetate (Note 9). This ethyl acetate extract is combined with the

other organic extracts, and the resulting solution is dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure (Note 10). The residue is purified by flash column chromatography (230-400 mesh silica gel, 270 g, packed with hexanes and eluted with 7.5% ethyl acetate-hexanes) to afford 3.64 g (76%) of (R)- α -methylbenzenepropanal as an oil (Note 11). The enantiomeric excess (ee) of this product is determined to be 95% (Note 12).

B. (R)- β -Methylbenzenepropanol. A flame-dried, 1-L, three-necked, round-bottomed flask equipped with a large, football-shaped, Teflon-coated magnetic stirring bar is sealed under argon with three rubber septa, one containing a needle adapter to an argon-filled balloon. One septum is removed briefly while the reaction flask is charged with 150 mL of tetrahydrofuran (Note 6), and the septum is replaced, sealing the flask. The flask is cooled to -78°C in a dry ice-acetone bath. Diisopropylamine (18.9 mL, 135 mmol, Note 13) and 53.5 mL (125 mmol) of a 2.34 M solution of butyllithium in hexanes (Note 14), respectively, are added to the reaction flask. The resulting yellow solution is stirred at -78°C for 10 min, then at 0°C (ice-water bath) for 5 min, and finally is cooled to -78°C . After 10 min, one of the rubber septa is removed, 4.41 g (129 mmol) of solid 90% borane-ammonia complex (Note 15) is added to the cold reaction solution in one portion, and the flask is sealed again with a rubber septum. The resulting suspension is warmed to 0°C and is stirred at that temperature for 20 min, during which time gas evolution is observed, and a sticky, white foam develops (Note 16). The suspension is warmed to 23°C in order to facilitate stirring and, after 20 min, the suspension of lithium amidotrihydroborate³ is cooled to 0°C in an ice-water bath. After 10 min, a solution of 10.0 g (32.1 mmol) of (1S,2S)-pseudoephedrine-(R)-2-methylhydrocinnamamide (Note 5) in 150 mL of tetrahydrofuran is added to the suspension of lithium amidotrihydroborate via cannula over 3 min (Note 17). A quantitative transfer is effected with 5 mL of tetrahydrofuran. The ice-water bath is removed, and the reaction mixture is stirred at 23°C for 50 min.

The reaction mixture is cooled to 0°C, one of the septa is removed, and excess hydride is quenched by the cautious addition of 10-mL portions of 3 N aqueous hydrochloric acid solution (350 mL total) over 5 min (Note 18). The biphasic mixture is stirred at 23°C for 30 min, then poured into a 1-L separatory funnel. The aqueous layer is separated and extracted with three 150-mL portions of ether. The combined organic fractions are washed with 50 mL of 3 N aqueous hydrochloric acid solution followed by 50 mL of brine. The organic layer is dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure (Note 19). The residue is purified by flash column chromatography (230-400 mesh silica gel, 250 g, 43% ether-petroleum ether as eluent) to afford 4.35 g (90%) of analytically pure (R)- β -methylbenzenepropanol as a colorless oil (Note 20). The ee of this product is determined to be $\geq 95\%$ (Note 21).

C. (R)-2-Methyl-1-phenyl-3-heptanone. A flame-dried, 500-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with 10.0 g (32.1 mmol) of (1S,2S)-pseudoephedrine-(R)-2-methylhydrocinnamamide (Note 5) and 50 mL of toluene (Note 22). This mixture is warmed with a heat gun until a clear solution is obtained. The solvent is removed under reduced pressure to afford a powdery white residue (Note 23). The flask is flushed with argon, charged with 250 mL of ether (Note 24), and then sealed with a rubber septum containing a needle adapter to an argon-filled balloon. The reaction flask is cooled to -78°C in a dry ice-acetone bath and 32.3 mL (77.2 mmol) of a 2.39 M solution of butyllithium in hexanes (Note 14) is added slowly via syringe over 5 min. The reaction mixture is stirred for 5 min at -78°C after which time the dry ice-acetone bath is removed and replaced with an ice-water bath. During the course of warming to 0°C, the reaction suspension clears to form a yellow solution. After 15 min at 0°C, 4.5 mL (32 mmol) of diisopropylamine (Note 13) is added to the reaction mixture to scavenge any excess butyllithium. After 15 min further stirring at 0°C, 100 mL of a solution of acetic acid (20% v/v) in ether is added as a final quench, producing a white flocculent precipitate. The mixture is transferred to a 1-L

separatory funnel with 300 mL of water and 300 mL of ethyl acetate. After vigorous mixing, the phases are allowed to separate, giving two clear, colorless layers. The aqueous layer is separated and extracted with two 300-mL portions of dichloromethane. The combined organic extracts are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (230-400 mesh silica gel, 350 g, graded elution with 2 → 5% ethyl acetate-hexanes) yields 5.80 g (88%) of analytically pure (R)-2-methyl-1-phenyl-3-heptanone (Notes 25, 26). The ee of this product is determined to be $\geq 95\%$ (Notes 27, 28).

2. Notes

1. Lithium aluminum hydride (95%) was obtained from Aldrich Chemical Company, Inc., and was stored under an atmosphere of nitrogen.

2. Hexanes used in the preparation of $\text{LiAlH}(\text{OEt})_3$ was distilled from calcium hydride under an atmosphere of nitrogen.

3. Ethyl acetate used in the preparation of $\text{LiAlH}(\text{OEt})_3$ was distilled from calcium hydride under an atmosphere of argon.

4. Slow addition of ethyl acetate is crucial in order to achieve complete reaction in the reduction step. Rapid addition of ethyl acetate (≤ 5 min) results in incomplete reduction of the amide.

5. (1S,2S)-Pseudoephedrine-(R)-2-methylhydrocinnamamide was prepared as described in the preceding procedure.

6. Tetrahydrofuran was distilled from sodium benzophenone ketyl under an atmosphere of nitrogen.

7. Trifluoroacetic acid was obtained from Mallinckrodt, Inc., and was used without further purification.

8. This operation is necessary to hydrolyze the pseudoephedrine aminal which forms as a direct product of the reduction, in addition to the desired aldehyde. The use of the additional 700 mL of 1 N aqueous hydrochloric acid solution was found to be crucial for this hydrolysis reaction.

9. The pH of the aqueous phase following the addition of sodium bicarbonate is approximately 4. If the pH is less than 4, additional sodium bicarbonate should be added until the pH is 4 or slightly above. Small amounts of the pseudoephedrine aminal remain at this point, but are hydrolyzed during the rotary evaporation step.

10. Rotary evaporation was conducted at or below 30°C to prevent trifluoroacetic acid-induced decomposition of the aldehyde as well as its evaporative loss.

11. The product exhibits the following properties: $[\alpha]_D^{25} +13.3^\circ$ (MeOH, *c* 0.46); ^1H NMR (300 MHz, C_6D_6) δ : 0.69 (d, 3 H, *J* = 6.9), 2.0-2.2 (m, 2 H), 2.72 (dd, 1 H, *J* = 13.2, 5.4), 6.8-7.1 (m, 5 H), 9.29 (d, 1 H, *J* = 1.2); ^{13}C NMR (75 MHz, CDCl_3) δ : 13.1, 36.5, 48.0, 126.3, 128.4, 128.9, 138.7, 204.3; IR (neat) cm^{-1} : 3028, 2971, 2932, 2814, 2716, 1723 (C=O), 1496, 1454, 742, 701; HRMS (EI) *m/z* 148.0890 [(*M*⁺) calcd for $\text{C}_{10}\text{H}_{12}\text{O}$: 148.0888]. Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{O}$: C, 81.04, H, 8.16. Found: C, 80.98, H, 8.25.

12. The ee of this product was determined by oxidation⁴ to the corresponding carboxylic acid (see following paragraph) followed by preparation and analysis of the corresponding (R)- α -methylbenzylamide.

A 25-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with 26 mg (0.18 mmol) of (R)- α -methylbenzenepropanal, 4.0 mL of 2-methyl-2-propanol, 1.0 mL (2.0 mmol) of a 2.0 M solution of 2-methyl-2-butene in tetrahydrofuran (purchased from Aldrich Chemical Company, Inc., and used as received), and a solution of 0.17 g (1.9 mmol) of sodium chlorite (Aldrich Chemical Company, Inc.; 80% technical grade) and 0.20 g (1.4 mmol) of sodium dihydrogen

phosphate monohydrate (Aldrich Chemical Company, Inc.) in 2.0 mL of water. The reaction flask is sealed with a rubber septum and the yellow, biphasic mixture is stirred vigorously at 23°C for 50 min, then partially concentrated by the removal of tetrahydrofuran, 2-methyl-2-butene, and 2-methyl-2-propanol on the rotary evaporator. The residue is transferred to a 125-mL separatory funnel with 50 mL of water and 0.5 mL of saturated aqueous sodium bicarbonate solution and the aqueous mixture is extracted with two 7-mL portions of 10% ethyl acetate-hexanes. The aqueous phase is acidified to pH 2 by the addition of 1.5 mL of 1 N aqueous hydrochloric acid solution, and the acidified solution is extracted with three 15-mL portions of ethyl acetate. The latter ethyl acetate extracts are combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 27 mg of crude (R)- α -methylbenzenepropanoic acid. The corresponding (R)- α -methylbenzylamide was prepared and analyzed by capillary gas chromatography as described in the following paragraph.

The following procedure describes the preparation and analysis of the (R)- α -methylbenzylamide of (R)- α -methylbenzenepropanoic acid. A flame-dried, 10-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a rubber septum is charged with 25 mg (0.15 mmol) of (R)- α -methylbenzenepropanoic acid, 31 mg (0.23 mmol) of 1-hydroxybenzotriazole hydrate, 44 mg (0.23 mmol) of 1-(3-dimethylamino)propyl-3-ethylcarbodiimide hydrochloride, and 0.50 mL of anhydrous N,N-dimethylformamide. This mixture is stirred at 23°C for 10 min, then cooled to 0°C in an ice-water bath. To the cooled solution, 24 μ L (0.19 mmol) of R-(+)- α -methylbenzylamine and 86 μ L (0.62 mmol) of triethylamine are added. Within 1 min, a fine white precipitate appears. The mixture is stirred for 1 hr at 0°C, then warmed to 23°C. After stirring for 20 hr at 23°C, the mixture is transferred to a 30-mL separatory funnel with 10 mL of dichloromethane. The product solution is extracted, sequentially, with four 10-mL portions of 1 N aqueous hydrochloric acid solution, 10 mL of saturated

aqueous sodium bicarbonate solution, and 10 mL of water. The organic layer is dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford a white crystalline solid. The solid residue is dissolved in ethyl acetate for capillary gas chromatographic analysis. The analysis is carried out using a Chirasil-Val capillary column (25 m x 0.25 mm x 0.16 μ m, Alltech, Inc.) under the following conditions: oven temp. 180°C, injector temp. 250°C, detector temp. 275°C. The following retention times are observed: 10.55 min (major diastereomer), 11.61 min (minor diastereomer). It should be noted that the retention times can vary greatly depending on the age and condition of the column. 1-Hydroxybenzotriazole hydrate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, N,N-dimethylformamide and R-(+)- α -methylbenzylamine were purchased from Aldrich Chemical Company, Inc. and used without further purification. Triethylamine was purchased from Aldrich Chemical Company, Inc. and was distilled from calcium hydride under an atmosphere of nitrogen.

13. Diisopropylamine was obtained from Aldrich Chemical Company, Inc., and distilled from calcium hydride under an atmosphere of nitrogen.

14. Butyllithium (2.5 M solution in hexanes) was purchased from Aldrich Chemical Company, Inc., and titrated against diphenylacetic acid.⁵

15. Borane-ammonia complex (90%) was obtained from Aldrich Chemical Company, Inc., and stored and transferred under nitrogen.

16. The foam is found to impede, but not prevent, magnetic stirring.

17. As the addition proceeds, the foam dissipates and stirring becomes increasingly more facile.

18. In addition to quenching excess hydride, the acidification and subsequent extraction steps remove pseudoephedrine and any tertiary amine reaction by-product; the latter is otherwise difficult to remove by column chromatography.

19. The residue contains (R)- β -methylbenzenepropanol and an alkoxy borane species that undergoes quantitative hydrolysis to (R)- β -methylbenzenepropanol during the subsequent chromatography step. As an alternative to flash column chromatography, the alkoxy borane species can be cleaved by treatment of the residue with 1 N aqueous sodium hydroxide solution.

20. The product exhibits the following properties: $[\alpha]_D^{25} +11.2^\circ$ (benzene, c 4.2); ^1H NMR (300 MHz, C_6D_6) δ : 0.62 (t, 1 H, $J = 5.2$), 0.77 (d, 3 H, $J = 6.7$), 1.70 (m, 1 H), 2.22 (dd, 1 H, $J = 13.3, 8.0$), 2.62 (dd, 1 H, $J = 13.3, 6.2$), 3.15 (m, 2 H), 7.0-7.2 (m, 5 H); ^{13}C NMR (75 MHz, CDCl_3) δ : 16.4, 37.7, 39.6, 67.4, 125.7, 128.2, 129.0, 140.6; IR (neat) cm^{-1} : 3332 (OH), 3001, 2956, 2922, 2872, 1603, 1495, 1454, 1378, 1032, 986, 739, 700; HRMS (CI) m/z 148.0890 $[(M + \text{NH}_4^+)]$. Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{O}$: C, 79.96; H, 9.39. Found: C, 79.67; H, 9.05.

21. The ee of the alcohol was determined by analysis of the corresponding Mosher ester derivative⁶ by high resolution ^1H NMR spectroscopy (400 MHz, C_6D_6). The preparation of the Mosher ester is described below.

A 10-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with 40 mg (0.17 mmol) of (R)-(+)- α -methoxy- α -(trifluoromethyl)-phenylacetic acid. Dry benzene (2 mL) is added and the resulting solution is concentrated. The flask is sealed with a rubber septum containing a needle adapter to an argon-filled balloon and is charged with 1.0 mL of dichloromethane. To the resulting clear solution is added 19 μL (0.22 mmol) of oxalyl chloride and 2.0 μL (0.026 mmol) of anhydrous N,N -dimethylformamide. The latter addition causes bubbling, which persists for ~10 min. The mixture is stirred an additional 20 min at 23°C , then cooled to 0°C in an ice-water bath. The adapter to the argon-filled balloon is replaced with a needle leading to a source of vacuum and the flask is cautiously evacuated. After 30 min stirring under reduced pressure (0.5 mm) to remove dichloromethane and excess oxalyl chloride, the flask is flushed with argon. The

resulting crude preparation of (S)-(+)- α -methoxy- α -(trifluoromethyl)phenylacetyl chloride is dissolved in 1.0 mL of dichloromethane, and the resulting clear solution is transferred via cannula to an ice-cooled, 10-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a rubber septum and containing a solution of 9.0 mg (0.060 mmol) of (R)- β -methylbenzenepropanol, 2.0 mg (0.016 mmol) of 4-dimethylaminopyridine, and 42 μ L (0.30 mmol) of triethylamine in 0.5 mL of dichloromethane. The ice-water bath is removed, and the clear yellow reaction solution is stirred at 23°C for 24 hr. The reaction mixture is transferred to a 30-mL separatory funnel with 10 mL of dichloromethane, and the solution is extracted, sequentially, with two 10-mL portions of saturated aqueous ammonium chloride solution, two 10-mL portions of saturated aqueous sodium bicarbonate solution, and 10 mL of water. The organic layer is dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil. The residue is purified by passage through a Pasteur pipette half-filled with 230-400 mesh silica gel using 30% ethyl acetate-hexanes as the eluent. Care is taken to collect all fractions containing the Mosher ester. Concentration of these fractions under reduced pressure affords a clear, colorless oil that is analyzed by ^1H NMR spectroscopy (400 MHz, C_6D_6). Integration of a pair of doublets of doublets corresponding to the major diastereomer (3.97-4.04 ppm and 3.76-3.82 ppm) against those corresponding to the minor diastereomer (3.86-3.95 ppm) allows accurate determination of the ee of the original alcohol. (R)-(+)- α -Methoxy- α -(trifluoromethyl)phenylacetic acid, oxalyl chloride, 4-dimethylaminopyridine, and anhydrous N,N-dimethylformamide were obtained from Aldrich Chemical Company, Inc., and were used without further purification. Benzene and dichloromethane used in the preparation of the Mosher ester were obtained from EM Science and were distilled from calcium hydride under a nitrogen atmosphere.

22. Toluene was purchased from EM Science and was distilled from calcium hydride under a nitrogen atmosphere.

23. This step is conducted to dry the amide, as well as to render it a fine powder.

24. Ether was purchased from EM Science and was distilled from sodium benzophenone ketyl under a nitrogen atmosphere.

25. This product exhibits the following properties: $[\alpha]_D^{25} -79.0^\circ$ (benzene, *c* 2.1); ^1H NMR (300 MHz, C_6D_6) δ : 0.85 (t, 3 H, *J* = 7.3), 1.07 (d, 3 H, *J* = 6.9), 1.23 (sx, 2 H, *J* = 7.4), 1.45 (m, 2 H), 2.25 (dt, 1 H, *J* = 7.3, 16.9), 2.39 (dt, 1 H, *J* = 7.3, 16.9), 2.55 (dd, 1 H, *J* = 7.3, 13.2), 2.83 (sx, 1 H, *J* = 7.0), 2.97 (dd, 1 H, *J* = 7.1, 13.2), 7.20 (m, 5 H); ^{13}C NMR (75 MHz, CDCl_3) δ : 13.9, 16.5, 22.3, 25.6, 39.1, 41.7, 48.1, 126.2, 128.3, 128.9, 139.8, 214.4; IR (neat) cm^{-1} : 3028, 2959, 2932, 2873, 1947, 1878, 1805, 1712 ($\text{C}=\text{O}$), 1604, 1496, 1454, 1406, 1375, 1130, 1032, 992, 746, 700; HRMS (EI) *m/z* 204.1517 $[(\text{M})^+]$ calcd for $\text{C}_{14}\text{H}_{20}\text{O}$: 204.1514]. Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}$: C, 82.30; H, 9.87. Found: C, 82.14; H, 9.59.

26. The checkers also obtained 2-3% of (R)-3-butyl-2-methyl-1-phenylheptan-3-ol, resulting from addition of 2 equiv of butyllithium to the amide carbonyl. This by-product stains brightly on analytical TLC plates (phosphomolybdic acid or cerium molybdate stain) and has an R_f of 0.2 in 5% EtOAc-hexanes.

27. The ee of this product was determined by reduction to the corresponding alcohol with lithium aluminum hydride followed by preparation and analysis of the Mosher ester derivatives⁶ by ^1H NMR spectroscopy (400 MHz, C_6D_6), as described in the following paragraph.

A flame-dried, 10-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with 102 mg (0.50 mmol) of (R)-2-methyl-1-phenyl-3-heptanone and sealed with a rubber septum containing a needle adapter to an argon-filled balloon. The flask is charged with 1.0 mL of ether and cooled to 0°C whereupon 0.75 mL (0.75 mmol) of a solution of lithium aluminum hydride in ether (1.0 M) is added slowly via syringe. After stirring the reaction mixture for 15 min at 0°C , the septum is removed and 1 mL of water is added cautiously dropwise until gas evolution

subsides. To the resulting cloudy mixture is added 2 mL of 15% w/v aqueous sodium hydroxide solution. This mixture is transferred to a 30-mL separatory funnel with 10 mL of water, and the resulting solution is extracted with three 10-mL portions of dichloromethane. The combined organic extracts are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. This crude preparation of diastereomeric alcohols (ca. 1:1 ratio) is used directly in the subsequent esterification step with the Mosher acid chloride, as described below.

A 0.3 M solution (0.50 mL, 0.15 mmol) of R-(+)- α -methoxy- α -(trifluoromethyl)-phenylacetyl chloride in dichloromethane is transferred via cannula to an ice-cooled, 10-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and containing a solution of 10 mg (0.05 mmol) of the crude alcohol, 6 mg (0.05 mmol) of 4-dimethylaminopyridine, and 71 μ L (0.51 mmol) of triethylamine in 1.0 mL of dichloromethane. The ice-water bath is removed, and the clear yellow reaction solution is stirred at 23°C for 24 hr. The reaction mixture is transferred to a 30-mL separatory funnel with 10 mL of dichloromethane, and the solution is extracted, sequentially, with two 10-mL portions of saturated aqueous ammonium chloride solution, two 10-mL portions of saturated aqueous sodium bicarbonate solution, and 10 mL of water. The organic layer is dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil. The residue is purified by passage through a Pasteur pipette half-filled with 230-400 mesh silica gel using 30% ethyl acetate-hexanes as the eluent. Care is taken to collect all fractions containing the Mosher esters. Concentration of these fractions under reduced pressure affords a clear, colorless oil that is analyzed by ^1H NMR spectroscopy (400 MHz, C_6D_6). Integration of a pair of doublets of doublets corresponding to the major diastereomer pairs (2.67 ppm) against those corresponding to the minor diastereomer pairs (2.74 ppm) allows accurate determination of the ee of the original ketone. 1.0 M Lithium aluminum hydride solution in ether and 4-dimethylaminopyridine were obtained from

Aldrich Chemical Company, Inc., and were used without further purification. Dichloromethane used in the preparation of the Mosher ester was obtained from EM Science and was distilled from calcium hydride under a nitrogen atmosphere. (R)-(-)- α -Methoxy- α -(trifluoromethyl)phenylacetyl chloride was prepared from (S)-(-)- α -methoxy- α -(trifluoromethyl)phenylacetic acid, as described in Note 21.

28. The ee determined by the checkers was 97% ee.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

These procedures illustrate the various methods used to transform pseudoephedrine amides into highly enantiomerically enriched aldehydes, alcohols, and ketones, and are applicable over a wide range of pseudoephedrine amide substrates.^{7,8} Reduction of pseudoephedrine amides to the corresponding aldehydes is best achieved using Brown and Tsukamoto's lithium triethoxyaluminum hydride reagent,² whereas reduction to the corresponding primary alcohols is best achieved with a new reagent, lithium amidotrihydroborate (LAB).³ In connection with the preceding procedure describing the synthesis and alkylation of pseudoephedrine amides, these methods provide access to a wide range of useful optically active synthetic intermediates in a highly practical manner.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(R)- α -Methylbenzenepropanal: Benzenepropanal, α -methyl-, (R)- (9); (42307-59-5)

Lithium aluminum hydride: Aluminate (1-), tetrahydro-, lithium (8); Aluminate (1-), tetrahydro-, lithium, (1-4)- (9); (16853-85-3)

Ethyl acetate: Acetic acid, ethyl ester (8,9); (141-78-6)

[1S(R),2S]-N-(2-Hydroxy-1-methyl-2-phenylethyl)-N, 2-dimethylbenzene propionamide: (1S,2S)-Pseudoephedrine-(R)-2-methylhydrocinnamide: Benzenepropanamide, N-(2-hydroxy-1-methyl-2-phenylethyl)-N, α -dimethyl-, [1S-[1R*(R*),2R*]]- (13); (159345-08-1); [1S-[1R*(S*),2R*]]- (13); (159345-06-9)

Lithium triethoxyaluminum hydride: Aluminate (1-), triethoxyhydro-, lithium (8); Aluminate (1-), triethoxyhydro-, lithium, (1-4), (9); (17250-30-5)

Trifluoroacetic acid: Acetic acid, trifluoro- (8,9); (76-05-1)

(R)- β -Methylbenzenepropanol: Benzenepropanol, β -methyl-, (R)- (10); (77943-96-5)

Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Borane-ammonia complex: EXPLODES WHEN HEATED: Borane, monoammoniate (8,9); (13774-81-7)

Lithium amidotrihydroborate: Borate (1-), amidotrihydro-, lithium, (I-4)- (11); (99144-67-9)

(R)-2-Methyl-1-phenyl-3-heptanone: 3-Heptanone, 2-methyl-1-phenyl-, (R)- (13); (159213-12-4)

2-Methyl-2-propanol: tert-Butyl alcohol (8); 2-Propanol, 2-methyl- (9); (75-65-0)

2-Methyl-2-butene: 2-Butene, 2-methyl- (8,9); (513-35-9)

Sodium dihydrogen phosphate: Phosphoric acid, monosodium salt (8,9); (7558-80-7)

(R)- α -Methylbenzenepropanoic acid: Benzenepropanoic acid, α -methyl-, (R)- (8); (14367-67-0)

1-Hydroxybenzotriazole hydrate: 1H-Benzotriazole, 1-hydroxy-, hydrate (12); (12333-53-9)

1-(3-Dimethylamino)propyl-3-ethylcarbodiimide hydrochloride: Carbodiimide, [3-(dimethylamino)propyl]ethyl-, monohydrochloride (8); 1,3-Propanediamine, N'-(ethylcarbonimidoyl)-N,N-dimethyl-, monohydrochloride (9); (25952-53-8)

N,N-Dimethylformamide: CANCER SUSPECT AGENT: Formamide, N,N-dimethyl- (8,9); (68-12-2)

(R)-(+)- α -Methylbenzylamine: Benzylamine, α -methyl-, (R)-(+)- (8); Benzenemethanamine, α -methyl-, (R)- (9); (3886-69-9)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

(R)-(+)- α -Methoxy- α -(trifluoromethyl)phenylacetic acid: Hydratropic acid, β,β,β -trifluoro- α -methoxy-, (+)- (9); (20445-31-2)

Benzene: CANCER SUSPECT AGENT: (8,9); (71-43-2)

Oxalyl chloride (8); Ethanedioyldichloride (9); (79-37-8)

(S)-(+)- α -Methoxy- α -(trifluoromethyl)phenylacetyl chloride: Hydratropoyl chloride, β,β,β -trifluoro- α -methoxy-, (+)- (8,9); (20445-33-4)

4-Dimethylaminopyridine: HIGHLY TOXIC: Pyridine, 4-(dimethylamino)- (8);

4-Pyridinamine, N,N-dimethyl- (9); (1122-58-3)

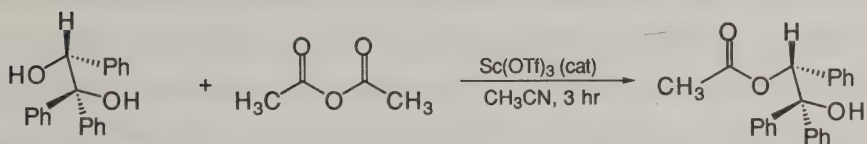
Phosphomolybdic acid: Molybdophosphoric acid (9); (51429-74-4)

Cerium (III) molybdate: Molybdic acid, cerium salt (9); (53986-44-0)

(S)-(-)- α -Methoxy- α -(trifluoromethyl)phenylacetic acid: Hydratropic acid, β,β,β -trifluoro- α -methoxy-, (S)-(-)- (8); Benzeneacetic acid, α -methoxy- α -(trifluoromethyl)-, (S)- (9); (17257-71-5)

(R)-(+)-2-HYDROXY-1,2,2-TRIPHENYLETHYL ACETATE

(1,2-Ethanediol, 1,1,2-triphenyl-, 2-acetate, (R)-)



Submitted by John Macor, Anthony J. Sampognaro, Patrick R. Verhoest, and Robert A. Mack.¹

Checked by Christoph Gaul and Stephen F. Martin.

1. Procedure

(R)-(+)-2-Hydroxy-1,2,2-triphenylethyl acetate [(R)-HYTRA]. To a mechanically stirred solution of (R)-(+)-1,1,2-triphenyl-1,2-ethanediol (35.0 g, 0.121 mol, Note 1) and acetic anhydride (17.1 mL, 0.181 mol, 1.5 eq, Note 2) in anhydrous acetonitrile (500 mL, Note 3) at room temperature under nitrogen is added a solution of scandium(III) trifluoromethanesulfonate (1.23 g, 2.5 mmol, 2 mol%, Note 4) in anhydrous acetonitrile (125 mL) over approximately 35 min (Note 5). After about 8 min a white precipitate begins to appear, and the resulting mixture is stirred at room temperature under nitrogen for a total of 3 hr. The solid is filtered, washed with acetonitrile (2 x 25 mL), and dried under vacuum at 40°C overnight to afford (R)-(+)-2-hydroxy-1,2,2-triphenylethyl acetate (35.42 g, 0.107 mol, 88%) as a white solid (Note 6).

2. Notes

1. Commercially available 1,1,2-triphenyl-1,2-ethanediol in either antipode can be used. The checkers used (R)-(+)-1,1,2-triphenyl-1,2-ethanediol from Aldrich Chemical Company, Inc., ($[\alpha]_D^{20} +210^\circ$ (C₂H₅OH, *c* 1). Alternatively, 1,1,2-triphenyl-1,2-ethanediol can be prepared via the procedure in *Organic Syntheses*.^{2d}

2. Acetic anhydride was purchased from Aldrich Chemical Company, Inc., (99+% purity), and used without additional purification. A 50% excess of acetic anhydride is needed for the reaction to be complete in a reasonably short period of time. Greater than a 50% excess of acetic anhydride does not appreciably improve the reaction time to completion.

3. Acetonitrile was purchased from Aldrich Chemical Company, Inc., (anhydrous, 99.8% purity in SureSealTM bottles) and used without additional purification.

4. Scandium(III) trifluoromethanesulfonate [Sc(OTf)₃] was purchased from Aldrich Chemical Company, Inc., (99% purity) and used without additional purification.

5. The order of addition of the reagents has a significant effect on the yield of the reaction. The optimal order of addition of reagents is described above (i.e., addition of Sc[III](OTf)₃ slowly, last). Continual addition of the scandium(III) triflate during the course of the reaction maintained the pace of the process. Bolus addition of the catalyst resulted in a reaction that slowed down or stopped part way, resulting in lower yields. Premixing the Sc[III](OTf)₃ with the diol and adding the acetic anhydride last led to reproducibly lower yields of (R)-HYTRA and a longer time to precipitation of (R)-HYTRA. Absolutely seminal to the reaction was the choice of solvent since all starting materials were soluble in acetonitrile, whereas the product acetate was not, thus allowing purification by simple filtration.

6. Spectral data are as follows: mp 198-200°C (crude product); $[\alpha]_D^{22} +196^\circ$ (pyridine, crude product, *c* 1); mp 213-221°C (benzene);² $[\alpha]_D^{22} +201^\circ$ (pyridine, *c* 1); ¹H NMR (CDCl₃, 300 MHz) δ : 1.97 (s, 3 H), 2.80 (s, 1 H), 6.66 (s, 1 H), 7.01-7.16 (m, 10 H), 7.24-7.38 (m, 3 H), 7.52-7.56 (m, 2 H); ¹³C NMR (CDCl₃, 125 MHz) δ : 21.1, 78.5, 80.3, 126.2, 126.3, 127.0, 127.3, 127.5, 127.8, 127.9, 128.4, 128.5, 135.9, 142.7, 144.8, 169.7; IR (CHCl₃) cm⁻¹: 3064, 3024, 1737, 1495, 1372, 1239, 1168, 779; HRMS calcd for C₂₂H₁₉O₂ ([MH⁺]-H₂O), *m/z* 315.1385, found 315.1386.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The (R)- and (S)-HYTRA (2-Hydroxy-1,2,2-Triphenylethyl Acetate) esters have been used in the diastereoselective addition of a chiral acetate to chiral and prochiral electrophiles, usually aldehydes.³ The generality of this reaction led to the commercialization of these agents and the precursor 1,1,2-triphenyl-1,2-ethanediols. Furthermore, Braun, Gräf, and Herzog had previously detailed a 100-plus-g synthesis.^{2d} However, the HYTRA esters are costly,⁴ and the synthesis previously reported was straightforward until the final step, in which acetyl chloride reacted with the 1,1,2-triphenyl-1,2-ethanediol to produce the HYTRA ester.^{2d} In this procedure, the HYTRA acetate was prepared in 92% yield (108 g), but the reaction work up was tedious and time consuming. To purify the HYTRA ester in this procedure, the reaction mixture is quenched with water, reaction solvent (CH₂Cl₂) is removed by evaporation under reduced pressure, and the resulting solids are filtered, washed with water, and

then transferred to a flask with toluene. Water is removed from the solid by an azeotropic distillation using toluene. The product is finally filtered from toluene to yield the acetate.

Yamamoto and co-workers reported the use of scandium(III) triflate as an esterification catalyst when acetic anhydride was used as the acetate source.^{5,6} While they only reported on monoalcohols (1°, 2°, and 3°) on a small scale, the submitters modified the Yamamoto procedure to suit the submitters' reaction with the 1,1,2-triphenyl-1,2-ethanediol. As detailed above, the current procedure provides a yield of the HYTRA acetate that is comparable to the procedure reported by Braun and co-workers,^{2d} but via simple, direct filtration for the reaction mixture.

1. Astra Zeneca, Three Biotech, One Innovation Drive, Worcester, MA 01605. Present address for J. M.: Bristol-Myers Squibb, Pharmaceutical Research Institute, P. O. Box 4000, Princeton, NJ 08543.
2. Several different melting points are reported in literature: (a) m.p. 220-221°C (from diethyl ether), Polansky, O.; Schinzel, E.; Wessely, F. *Monatsh. Chem.* **1956**, 87, 24-46; (b) mp 220-220.5°C (from diethyl ether/CH₂Cl₂), Corey, E. J.; Casanova, J. *J. Am. Chem. Soc.* **1963**, 85, 165-169; (c) 224.5-225.5°C (from benzene), Ito, N.; Nishino, H.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1983**, 56, 3527-3528; (d) 249-251°C (from toluene), Braun, M.; Gräf, S.; Herzog, S. *Org. Synth., Coll. Vol. IX* **1998**, 507.
3. Braun, M.; Gräf, S. *Org. Synth., Coll. Vol. IX* **1998**, 497, and references cited therein.
4. (R)-HYTRA ester in the 1998-1999 Aldrich Chemical Company catalog (p. 1499, item 37,650-7) is \$29.10/g.

5. Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 4413-4414.
6. Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560-4567.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(R)-(+)-2-Hydroxy-1,2,2-triphenylethyl acetate: [(R)-HYTRA]: 1,2-Ethanediol, 1,1,2-triphenyl-, 2-acetate, (R)- (11); (95061-47-5)

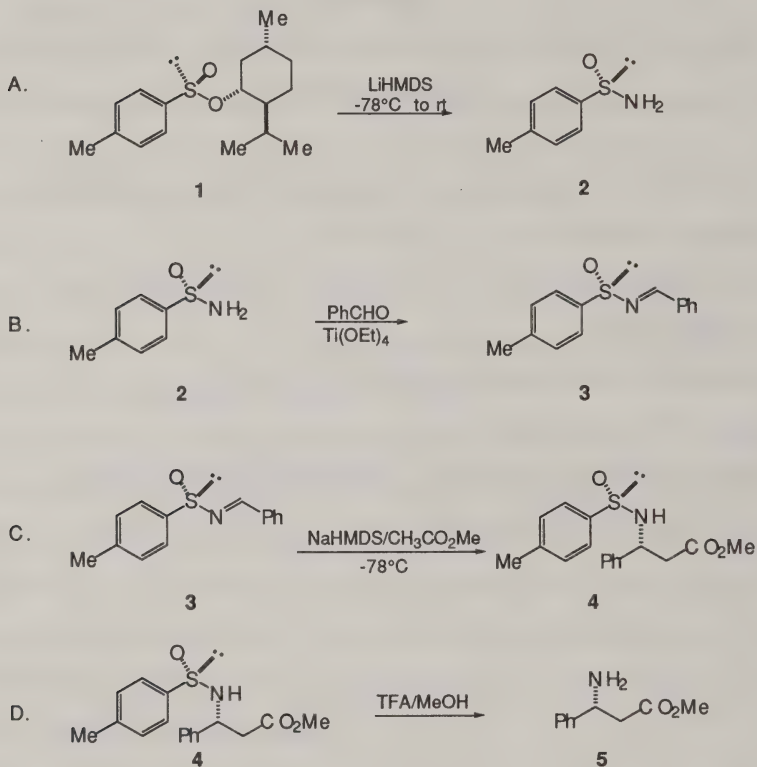
(R)-(+)-1,1,2-Triphenylethanediol: 1,2-Ethanediol, 1,1,2-triphenyl-, (R)- (11); (95061-46-4)

Acetic anhydride (8); Acetic acid anhydride (9); (108-24-7)

Acetonitrile: TOXIC: (8,9); (75-05-8)

Scandium(III) trifluoromethanesulfonate: Methanesulfonic acid, trifluoro-, scandium (3+) salt (13); (144026-79-9)

**SULFINIMINES (THIOOXIMINE S-OXIDES): ASYMMETRIC SYNTHESIS
OF METHYL (R)-(+)- β -PHENYLALANATE FROM (S)-(+)-N-
(BENZYLIDENE)-p-TOLUENESULFINAMIDE
(Benzenepropanoic acid, β -amino-, (R)-, methyl ester from
Benzenesulfinamide, 4-methyl-N-(phenylmethylene)- [S-(E)]-)**



Submitted by Dean L. Fanelli, Joanna M. Szewczyk, Yulian Zhang, G. Venkat Reddy,
David M. Burns, and Franklin A. Davis.¹

Checked by James Unch and David J. Hart.

1. Procedure

A. *(S)-(+)-p-Toluenesulfinamide (2)*:² An oven-dried, 1-L, one-necked, round-bottomed flask (Note 1), equipped with a magnetic stirring bar and rubber septum is charged with 30.31 g (0.103 mol) of (1R,2S,5R)-(-)-menthyl (S)-p-toluenesulfinate (1) (Note 2) under an argon purge. The reaction flask is placed under vacuum for 1 hr to remove residual moisture, 220 mL of anhydrous tetrahydrofuran (Note 3) is added via cannula, and the solution is rapidly stirred and cooled to -78°C using a dry ice/acetone bath. To the white suspension (Note 4) is added 143.0 mL (0.143 mol) of 1.0 M lithium bis(trimethylsilyl)amide (LiHMDS) (Note 5) via syringe. The dry ice/acetone bath is removed and the solution is stirred for 4.5 hr at room temperature. The mixture is then cooled to -78°C in a dry ice/acetone bath, 30% aq ammonium chloride (120 mL) is added, and the mixture is warmed to room temperature. The solution is transferred to a 1-L separatory funnel, diluted with water (80 mL), and extracted with diethyl ether (3 x 160 mL). The combined organic phases are washed with water (2 x 120 mL), brine (120 mL), dried over anhydrous sodium sulfate, filtered into a 1-L, single-necked, round-bottomed flask, and concentrated using a rotary evaporator (Note 6). To the residual yellow paste is added pentane (100 mL). After standing overnight in the refrigerator (3°C), and warming to room temperature, the resulting solid is collected by suction filtration. The filter cake is rinsed with pentane (2 x 50 mL) and dried under vacuum to afford 11.52 g (72%) of analytically pure **2** as a white solid (Note 7).

B. *(S)-(+)-N-(Benzyldiene)-p-toluenesulfinamide (3)*:² An oven-dried, 500-mL, one-necked, round-bottomed flask (Note 1), equipped with a magnetic stirring bar and rubber septum is charged with 10.35 g (66.8 mmol) of (S)-(+)-p-toluenesulfinamide (2). The reaction flask is placed under vacuum (1 mm) for 30 min to remove residual moisture. The vessel is then placed under an argon atmosphere and dichloromethane (135 mL) (Note 8) is added via cannula. The solution is stirred rapidly and 7.07 g

(66.6 mmol) of benzaldehyde (Note 9) is added via syringe, followed by 76.0 g (333 mmol) of titanium(IV) ethoxide (Note 8) via cannula. The septum is removed, the solution is fitted with a reflux condenser topped with an argon gas line and the yellow solution is heated under reflux for 5 hr. The solution is cooled to room temperature and poured into water (85 mL) in a 600-mL beaker with rapid stirring (Note 10). Dichloromethane (50 mL) is added to the mixture, which is then filtered through a Buchner funnel using filter paper of medium porosity. The filter cake is rinsed with dichloromethane (3 x 70 mL). The filtrate is transferred to a 500-mL separatory funnel and washed with water (3 x 70 mL), brine (70 mL), dried over magnesium sulfate (MgSO_4) and filtered. The solution is concentrated using a rotary evaporator while keeping the bath temperature below 40°C to afford 15.0 g (92%) of analytically pure product as a white solid (Note 11).

C. (S_S,R)-(+)-Methyl N-(p-toluenesulfinyl)-3-amino-3-phenylpropanoate (4):³

An oven-dried, 250-mL, round-bottomed flask equipped with a magnetic stirrer and a rubber septum is charged with 8.4 mL of sodium bis(trimethylsilyl)amide (NaHMDS) (16.7 mmol) in tetrahydrofuran (Note 12). The reaction mixture is diluted with 80 mL of anhydrous ether (Note 13), the solution is cooled to -78°C using a dry ice/acetone bath, and 1.3 mL of methyl acetate (16.7 mmol) (Note 14) is added dropwise via syringe over 20 min. In a separate, oven-dried, 100-mL, round-bottomed flask, equipped with a magnetic stirrer, rubber septum and under an argon purge, is placed 2.65 g (10.9 mmol) of (S)-(+)-N-(benzylidene)-p-toluenesulfinamide (**3**) in 50 mL of anhydrous ether. The solution of **3** is cooled to 0°C and added by cannula over 60 min into the reaction flask containing the enolate. The flask is rinsed with 10 mL of anhydrous ether and cooled to -78°C prior to adding it to the reaction mixture by cannula. After the mixture is stirred for 45 min, it is quenched at this temperature with 4 mL of aqueous saturated ammonium chloride (Note 15), warmed to room temperature, and diluted with 50 mL of ethyl acetate. The solution is transferred to a 250-mL

separatory funnel, washed with water (2 x 50 mL), and the aqueous phases are combined and washed with ethyl acetate (2 x 20 mL). The combined organic phases are washed with aqueous saturated sodium chloride (2 x 40 mL), dried over anhydrous magnesium sulfate and filtered. The solution is concentrated using a rotary evaporator (33°C and 13 mm), followed by drying under high vacuum (30°C and 0.05 mm) to give a yellow solid (2.7 g) (mp 82-85°C). This material is dissolved in 5 mL of ethyl acetate and 5 mL of methylene chloride, diluted with 125 mL of pentane, and stored at -20°C overnight (Note 16). The slightly yellow suspended solid is filtered, washed with cold pentanes (2 x 15 mL; ca. -20°C), and dried under high vacuum to remove residual solvent to afford 2.1-2.3 g (61-66%) of analytically pure **4** (Notes 17, 18 and 19).

D. Hydrolysis of (S_S,R)-(+)-Methyl N-(p-tolylsulfinyl)-3-amino-3-phenylpropanoate (4): An oven-dried, 250-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with 2.13 g (6.7 mmol) of (S_S,R)-(+)-methyl N-(p-tolylsulfinyl)-3-amino-3-phenylpropanoate (**4**), sealed with a rubber septum, and 100 mL of methanol is added (Note 20). Stirring is initiated and the white mixture is cooled to 0°C, in an ice/water bath, prior to adding 1.9 mL (24.6 mmol) of trifluoroacetic acid (Note 21) via cannula over 3 min. After 10 min the solution is warmed to room temperature and stirred for 2-4 hr (Note 22). The solvent is removed using a rotary evaporator. The resulting yellow liquid is diluted with 15 mL of diethyl ether (Note 23) and transferred to a 250-mL separatory funnel. The flask is rinsed with diethyl ether (2 x 30 mL) and the combined organic phases are extracted with 15% aqueous hydrochloric acid (HCl) (2 x 75 mL) (Note 24). The combined aqueous HCl extracts are washed with diethyl ether (50 mL) (Note 25) and then transferred to a 400-mL beaker containing dichloromethane (50 mL) and a magnetic stirring bar. The solution is cooled to 0°C using an ice/water bath, and solid sodium bicarbonate (NaHCO₃) is carefully added to adjust the pH to 8 (Notes 26 and 27). The resulting emulsion is transferred to a 250-

mL separatory funnel, diluted with 25 mL of methylene chloride, and the aqueous layer is extracted with methylene chloride (3 x 50 mL). The organic phases are washed with 50 mL of water, saturated brine (2 x 50 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent on a rotary evaporator affords 0.99 g of crude methyl (R)-(+)- β -phenylalanate as a viscous yellow oil (Note 28). This material is purified by bulb-to-bulb distillation to give 0.813 g (68%) of **5** as a water white liquid (Note 29).

2. Notes

1. All glassware was predried at 120°C for at least 4 hr and cooled to room temperature prior to use in a desiccator.
2. (1R,2S,5R)-(-)-Menthyl (S)-p-toluenesulfinate was purchased from Aldrich Chemical Company, Inc., or can be prepared by the following procedures: (a) Hulce, M.; Mallamo, J. P.; Frye, L. L.; Kogan, T. P.; Posner, G. H. *Org. Synth., Coll. Vol. VII* **1990**, 495; (b) See also Reference 4.
3. Reagent grade tetrahydrofuran was freshly distilled under nitrogen from a purple solution of sodium and benzophenone.
4. Upon cooling to -78°C, the solution of (1R,2S,5R)-(-)-menthyl (S)-p-toluenesulfinate (**1**) forms a white milky precipitate.
5. Lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M) solution was purchased from Aldrich Chemical Company, Inc.
6. The submitters indicate that use of a high vacuum pump results in removal of most of the menthol at this point. The checkers used a standard rotary evaporator (33°C at 16 mm) and observed that the residual yellow paste retains the menthol.
7. The physical properties of (S)-(+)-p-toluenesulfonamide were as follows: mp 110-112°C; $[\alpha]_D^{20} +79.7^\circ$ (CHCl₃, c 1.2), IR (KBr) cm⁻¹: 3200, 3094; ¹H NMR (CDCl₃)

δ : 2.42 (s, 3 H), 4.33 (s, 2H), 7.32 (d, 2 H, $J = 8$), 7.64 (d, 2 H, $J = 8$); ^{13}C NMR (CDCl_3) δ : 21.3, 125.3, 129.5, 141.4, 143.4. Anal. Calcd for $\text{C}_7\text{H}_9\text{NOS}$: C, 54.18; H, 5.85. Found: C, 54.22; H, 5.86.

8. Anhydrous methylene chloride and titanium(IV) ethoxide (technical grade) were purchased from Aldrich Chemical Company, Inc., and used as received.

9. Benzaldehyde was used from a freshly opened bottle purchased from Aldrich Chemical Company, Inc.

10. A magnetic stirring bar is used for initial stirring. A thick slurry develops and when magnetic stirring becomes impossible, the mixture is stirred with a metal spatula for about 1 min.

11. The physical properties of (S)-(+)-N-(benzylidene)-p-toluenesulfinamide were as follows: mp 80-81°C ee >95%; $[\alpha]_{\text{D}}^{20} +122.8^\circ$ (CHCl_3 , c 1.2); IR (KBr) cm^{-1} : 3050, 1607, 1574, 1449, 1104, 1072; ^1H NMR (CDCl_3) δ : 2.4 (s, 3 H), 7.32 (d, 2 H, $J = 8.0$), 7.4-7.52 (m, 3 H), 7.64 (d, 2 H, $J = 8.0$), 7.81-7.86 (m, 2 H), 8.74 (s, 1 H); ^{13}C NMR (CDCl_3) δ : 21.5, 124.7, 128.8, 129.5, 129.7, 132.5, 133.7, 141.6, 141.7, 160.0. Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{NOS}$: C, 69.11; H, 5.39. Found: C, 68.84; H, 5.50.

12. Sodium bis(trimethylsilyl)amide in tetrahydrofuran (2.0 M) was purchased from Acros Chemical Company, Inc.

13. Reagent grade anhydrous ether was freshly distilled under argon from a purple solution of sodium and benzophenone.

14. Anhydrous methyl acetate was purchased from Aldrich Chemical Company, Inc., and used without further purification.

15. The submitters indicate that completion of the reaction is confirmed by TLC on silica gel using 50% ethyl acetate in hexanes as the eluant.

16. The submitters indicate that **4** can also be purified by flash chromatography using 25% ethyl acetate/hexanes on silica gel (30 g/g of crude product), Merck grade 60 (230-400 mesh) was purchased from Aldrich Chemical Company, Inc.

17. The submitters indicate that the observed yield was 89% when the reaction was carried out on a 1.0-g scale.

18. The diastereomeric excess was determined by ^1H NMR (300 MHz, CDCl_3) by evaluating the p-tolyl methyl group (major δ 2.41 ppm: minor δ 2.36 ppm) or carbomethoxy group (major δ 3.60 ppm: minor δ 3.64 ppm).

19. The spectral properties of (S_S ,R)-(+)-methyl N-(p-tolylsulfinyl)-3-amino-3-phenylpropanoate (**4**) are as follows: >98% de; $[\alpha]_{\text{D}}^{20}$ 116.84° (CHCl_3 , c. 1.74) [checkers recorded $[\alpha]_{\text{D}}^{18}$ 111.1° (CHCl_3 , c. 1.74)]; mp 88-89°C; IR (KBr) cm^{-1} : 3155, 1737, 1436, 1295, 1170, 1044, 804, 700; ^1H NMR (CDCl_3) δ : 2.41 (s, 3 H), 2.86 (d, 2 H, $J = 6.3$), 3.60 (s, 3 H), 4.90 (q, 1 H, $J = 6.1$), 5.01 (d, 1 H, $J = 5.4$), 7.28-7.45 (m, 7 H), 7.60 (d, 2 H, $J = 8.2$); ^{13}C NMR (CDCl_3) δ : 21.2, 41.9, 51.7, 54.7, 125.3, 127.1, 127.9, 128.6, 129.4, 140.3, 141.3, 142.1, 171.1; MS m/z 317 (M^+), 269, 196, 178, 139, 121, 104, 91, 77. Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_3\text{S}$: C, 64.33; H, 6.03. Found: C, 64.38; H, 6.12.

20. A freshly opened bottle of methanol (certified A.C.S., purchased from Aldrich Chemical Company, Inc.) was used without further purification or drying.

21. Trifluoroacetic acid 99% was purchased from Aldrich Chemical Company, Inc.

22. The submitters indicate that the reaction can be monitored for the formation of **5** by thin layer chromatography (silica gel; 50% EtOAc/ hexanes).

23. Reagent grade anhydrous ethyl ether was purchased from Aldrich Chemical Company, Inc.

24. Aqueous hydrochloric acid (37%) certified A.C.S. *PLUS* was purchased from Fisher Chemical Fisher Scientific and diluted to 15% with water.

25. The checkers find that this wash eliminates methyl p-toluenesulfinate as a contaminant in the crude product.

26. Certified A.C.S. grade methylene chloride was purchased from Aldrich Chemical Company, Inc. and used as received. Sodium bicarbonate A.C.S. grade was purchased from Fisher Scientific Company.

27. The final pH should be at least 8.0 (by pH paper) to ensure that all the salt has been deprotonated.

28. The checkers recorded $[\alpha]_D^{18} +18.9^\circ$ (CHCl_3 , c 1.85) for this material and noted some unidentified impurities in the ^1H NMR spectrum. The submitters indicate that 3 mL of methanol can be added to the yellow liquid followed by filtration to remove precipitated solids.

29. The spectral properties of this material are as follows: bp $55\text{--}60^\circ\text{C}$ (oven temperature) at 0.05 mm; $>98\%$ ee, $[\alpha]_D^{20} +22.6^\circ$ (CHCl_3 , c 1.85); IR (neat) cm^{-1} : 3378, 3026, 2950, 1734, 1603, 1436, 1171, 1020, 762, 700; ^1H NMR (CDCl_3) δ : 1.87 (br s, 2 H, exchangeable with D_2O), 2.66 (d, 2 H, $J = 6.9$), 3.68 (s, 3 H), 4.42 (t, 1 H, $J = 6.7$), 7.25–7.35 (m, 5 H); ^{13}C NMR (CDCl_3) δ : 43.9, 51.5, 52.5, 126.1, 127.3, 128.5, 144.6, 172.4. Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_2$: C, 67.00; H, 7.32. Found: C, 66.50; H, 7.41.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory", National Academy Press: Washington, DC, 1995

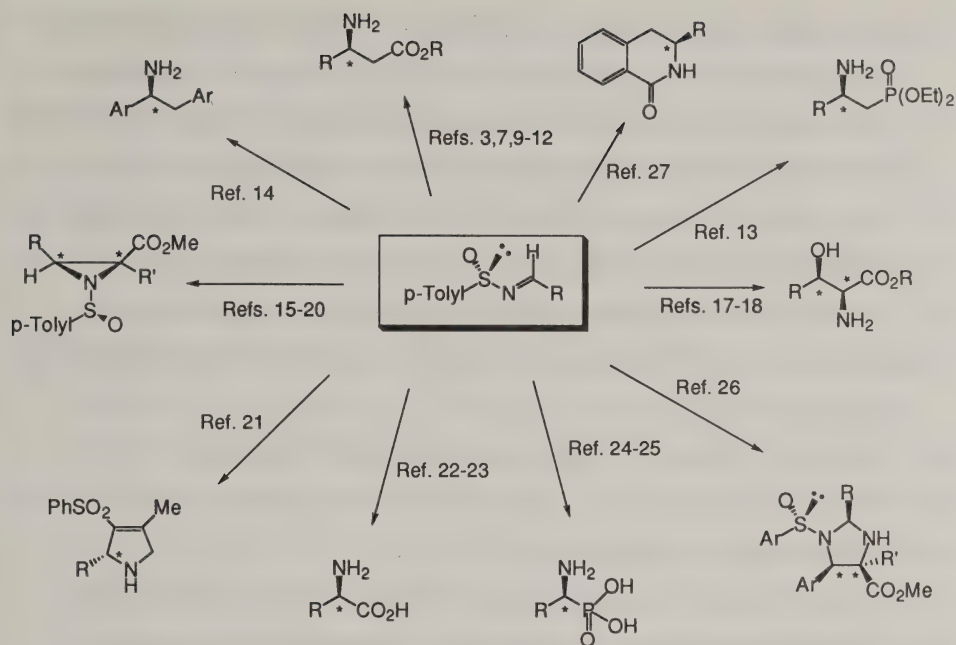
3. Discussion

Although the diastereoselective addition of nucleophiles to imines offers an attractive route to chiral amine derivatives, most chiral nonracemic imines suffer from low reactivity (electrophilicity), resulting in no reaction or competitive reduction with organometallic reagents. Other problems include enolization of aliphatic imines, poor

diastereoselectivities caused by syn/anti isomerism, and moisture sensitivity resulting in moderate or low yields. When primary amines are the objective, removing the N-auxiliary often leads to epimerization or destruction of the product.

The N-sulfinyl auxiliary in sulfinimines [ArS(O)-N=CHR, thiooxime S-oxides] offers a general solution for the control of imine reactivity and diastereoselectivity.⁵ In sulfinimines the electron-withdrawing N-sulfinyl group activates the C-N bond to such an extent that enolization of aliphatic examples is no longer a significant problem. Furthermore, the sulfinyl auxiliary exerts powerful stereodirecting effects in the addition of enolates and other organometallic reagents. Following separation of the diastereomeric sulfinamide [ArS(O)NH-CHRR'], hydrolysis affords the primary amine derivative without epimerization. Moreover, the sulfinamide N-sulfinyl group can be used for further elaboration of the product.

An earlier synthesis of sulfinimines, involving the addition of metal ketimines to the menthyl p-toluenesulfinate (Andersen reagent), was limited because an aromatic group was required to be present and the more valuable aldehyde-derived sulfinimines were unavailable.⁶ An asymmetric oxidation approach using chiral oxaziridines suffered from moderate ee's (<90%).⁷ tert-Butylsulfinimines are available in a series of steps starting with tert-butyl disulfide.⁸ The method described here affords these valuable building blocks from commercially available starting materials and aromatic and aliphatic aldehydes.² Although β -amino acids are less common than α -amino acids, they are important constituents of natural products, precursors of the β -lactams and increasingly used to modify proteins.⁹ The synthesis of β -phenylalanine methyl ester is an example of the general synthesis of this important class of amino acids using sulfinimines.^{3,6,10-12} Exclusive formation of the sulfinamide **4** is probably a consequence of the anion stabilizing N-sulfinyl group; analogous reactions of N-alkyl- and N-arylimines produce cyclized β -lactams. An added feature of the N-sulfinyl group in **4** is that it is easily removed under mild conditions.



Many other asymmetric syntheses of amine derivatives using enantiopure sulfinimines have been reported.²⁸⁻³³

1. Department of Chemistry, Temple University, Philadelphia, Pa 19122
2. Procedure adapted from Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403. For related chemistry see: Davis, F. A.; Reddy, R. E.; Szweczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Thimma Reddy, R.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl (R)-(+)- β -phenylalanate: Benzenepropanoic acid, β -amino-, (R)-, methyl ester (9); (37088-67-8)

(S)-(+)-N-(Benzyldiene)-p-toluenesulfinamide: Benzenesulfinamide, 4-methyl-N-(phenylmethylene)-, [S-(E)]- (13); (153277-49-7)

(S)-(+)-p-Toluenesulfinamide: Benzenesulfinamide, 4-methyl-, (S)- (14); (188447-91-8)

(1R,2S,5R)-(-)-Menthyl (S)-p-toluenesulfinate: Menthol, (-)-, (S)-p-toluenesulfinate (8); Benzenesulfinic acid, 4-methyl-, 5-methyl-2-(1-methylethyl)cyclohexyl ester, [1R-[1 α (S*),2 β ,5 α]]- (9); (1517-82-4)

Lithium bis(trimethylsilyl)amide: Disilazane, 1,1,1,3,3,3-hexamethyl-, lithium salt (8); Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, lithium salt (9); (4039-32-1)

Benzaldehyde (8,9); (100-52-7)

Titanium(IV) ethoxide: Ethyl alcohol, titanium(4+) salt (8); Ethanol, titanium(4+) salt (9); (3087-36-3)

(S_SR)-(+)-Methyl N-(p-toluenesulfinyl)-3-amino-3-phenylpropanoate:

Benzenepropanoic acid, β -[[[(4-methylphenyl)sulfinyl]amino]-, methyl ester, [S-(R*,S*)]-
(13); (158009-86-0)

Sodium bis(trimethylsilyl)amide: Disilazane, 1,1,1,3,3,3-hexamethyl-, sodium salt (8);

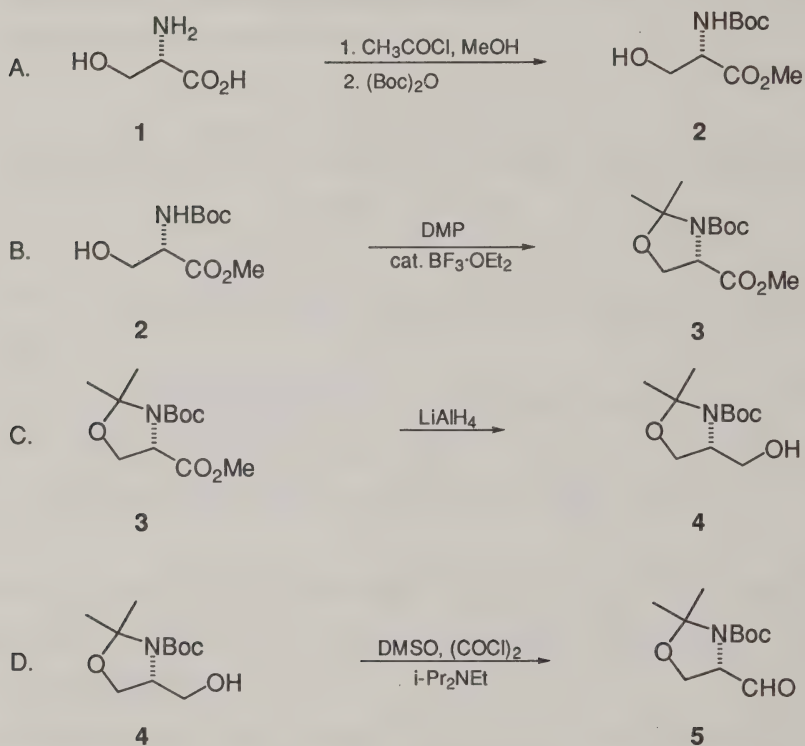
Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, sodium salt (9); (1070-89-9)

Methyl acetate: Acetic acid, methyl ester (8,9); (79-20-9)

Trifluoroacetic acid: Acetic acid, trifluoro- (8,9); (76-05-1)

**SYNTHESIS OF 1,1-DIMETHYLETHYL (S)-4-FORMYL-2,2-DIMETHYL-
3-OXAZOLIDINECARBOXYLATE BY OXIDATION
OF THE ALCOHOL**

(3-Oxazolidinecarboxylic acid, 4-formyl-2,2-dimethyl-, 1,1-dimethylethyl
ester, (S)-)



Submitted by Alessandro Dondoni and Daniela Perrone.¹

Checked by Mark M. Gleason and William R. Roush.

1. Procedure

A. *N*-[(1,1-Dimethylethoxy)carbonyl]-L-serine methyl ester (**2**). A 250-mL, three-necked, round-bottomed flask, containing a magnetic stirring bar, is equipped with a dropping funnel, reflux condenser protected from moisture by a calcium chloride-filled drying tube and a rubber septum (Note 1). The dropping funnel is charged with 23 mL of acetyl chloride (Note 2). *Caution! Acetyl chloride is a reactive substance that must be handled in a fume hood.* The flask is charged with 150 mL of methanol (Note 3) and cooled with an ice-water bath under nitrogen. Acetyl chloride is added dropwise over a period of 8 min. The solution is stirred for a further 5 min, then solid 99% (L)-serine, **1**, (12.0 g, 114 mmol, Note 4) is added in one portion and the solution is slowly heated to reflux. The reflux is continued for 2 hr, then the solution is allowed to cool to room temperature and the solvent is removed under reduced pressure to give 17.5-17.7 g of crude methyl serinate hydrochloride (98-99% yield) as a white crystalline solid that is used without further purification.

A 500-mL, three-necked, round-bottomed flask, is equipped with a magnetic stirring bar, thermometer, reflux condenser protected from moisture by a calcium chloride-filled drying tube, and a pressure-equalizing dropping funnel that is connected to a nitrogen flow line and is charged with a solution of 97% di-tert-butyl dicarbonate (14.3 g, 63.6 mmol) (Note 5) in tetrahydrofuran (100 mL, Note 6). Methyl serinate hydrochloride (10.0 g, 64.3 mmol) is placed in the flask and suspended in tetrahydrofuran (200 mL) and 99% triethylamine (14.0 g, 138 mmol, Note 7). The resulting white suspension is cooled with an ice-water bath and the solution of di-tert-butyl dicarbonate is added dropwise over a period of 1 hr. After 10 min of additional stirring, the ice-water bath is removed and the suspension is stirred overnight (14 hr) at room temperature, then warmed at 50°C for a further 3 hr. The solvent is removed under reduced pressure and the residue is partitioned between diethyl ether (200 mL)

and saturated aqueous bicarbonate solution (250 mL). The aqueous phase is extracted with three 150-mL portions of diethyl ether. The combined organic phases are dried with anhydrous sodium sulfate and concentrated under reduced pressure to give 13.4-14.0 g (95-99% crude yield) of N-Boc-L-serine methyl ester as a colorless oil that is used without further purification (Note 8).

B. 3-(1,1-Dimethylethyl) 4-methyl-(S)-2,2-dimethyloxazolidine-3,4-dicarboxylate (3). To a solution of N-Boc-L-serine methyl ester (10.0 g, 45.6 mmol) in acetone (165 mL) is added 2,2-dimethoxypropane (50 mL, 400 mmol) and boron trifluoride etherate ($\text{BF}_3 \cdot \text{OEt}_2$, 0.35 mL, 2.8 mmol) (Notes 9 and 10). The resulting orange solution is stirred at room temperature for 2.5 hr when TLC analysis indicates the reaction to be complete (Note 11). The reaction mixture is treated with 0.9 mL of 99% triethylamine and the solvent is removed under reduced pressure. The residual brown syrup is partitioned between diethyl ether (150 mL) and saturated aqueous sodium bicarbonate solution (250 mL). The aqueous layer is extracted with diethyl ether (2 x 150 mL) and the combined organic phases are dried with anhydrous sodium sulfate and concentrated under reduced pressure (7 mm and 65°C bath temperature) to give 10.4-10.8 g (88-91% crude yield) of oxazolidine methyl ester **3** as a pale yellow oil (Note 12). Analysis of crude **3** by ^1H NMR indicates a chemical purity of > 95%. The product can be used without further purification.

C. N-[(1,1-Dimethylethoxy)carbonyl]-N,O-isopropylidene-L-serinol (4). A 250-mL, two-necked, round-bottomed flask is equipped with a magnetic stirring bar, reflux condenser bearing a drying tube and a pressure-equalizing dropping funnel fitted with a rubber septum (Note 1). The flask is charged with 100 mL of tetrahydrofuran and 2.16 g (57.0 mmol) of lithium aluminum hydride (Notes 6 and 13). While the suspension in the flask is stirred, a solution of the oxazolidine ester **3** (9.90 g, 38.2 mmol) in tetrahydrofuran (50 mL) is added dropwise over 20 min. The dropping funnel is washed with two 3-mL portions of tetrahydrofuran and the suspension is stirred for

an additional 20 min, when TLC analysis shows the complete formation of the alcohol **4** (Note 14). The reaction mixture is cooled with an ice-water bath while 20 mL of a 10% aqueous potassium hydroxide solution is added dropwise over 10 min. *Caution! The reaction is exothermic.* The mixture is stirred for 1 hr at room temperature, then the white precipitate is removed by filtration through a Celite pad and the pad is rinsed with three 30-mL portions of diethyl ether. The combined organic filtrates are washed with 100 mL of aqueous phosphate buffer (pH 7) (Note 15), and the aqueous layer is extracted with diethyl ether (3 x 30 mL). The combined organic phases are dried with anhydrous sodium sulfate and concentrated under reduced pressure to give 8.20-8.48 g (93-96% crude yield) of a pale yellow oil. The crude product that solidifies on cold storage (mp 35-38°C) is used without further purification (Note 16). Analysis of crude alcohol **4** by ^1H NMR indicates a chemical purity of > 95%.

D. 1,1-Dimethylethyl (S)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate (5). A 250-mL, three-necked, round-bottomed flask, containing a magnetic stirring bar is equipped with a low-temperature thermometer and two equalizing dropping funnels (Note 1). One of these is connected to a nitrogen flow line and is charged with a solution of N-Boc-L-serinol **4** (8.0 g, 34.6 mmol) in methylene chloride (60 mL), the other is charged with a solution of dimethyl sulfoxide (8.10 g, 103.71 mmol) in 10 mL of methylene chloride (Notes 17 and 18). The flask is charged with a solution of oxalyl chloride (6.58 g, 51.9 mmol, Note 19) in 80 mL of methylene chloride, then cooled to -78°C in a CryoCool bath. *Caution! Oxalyl chloride is a reactive substance that must be handled in a fume hood.* When the solution in the flask is at -78°C, dimethyl sulfoxide is added dropwise over 25 min, while the temperature of the reaction mixture rises to -70°C. At the end of the addition the reaction solution is warmed to -60°C over a period of 20 min, then the N-Boc-L-serinol **4** is added dropwise over 50 min and the reaction temperature rises to -55°C. The dropping funnel is washed with two 5-mL portions of methylene chloride, then charged with a solution of N,N-

diisopropylethylamine (36 mL, 200 mmol, Note 20) in 5 mL of methylene chloride and the reaction solution is warmed to -45°C over a period of 30 min. N,N-Diisopropylethylamine is added over 5 min, then the reaction flask is removed from the CryoCool bath and allowed to warm to 0°C over 10 min. The reaction solution is transferred to a 500-mL separatory funnel charged with 130 mL of ice-cold 1 M hydrochloric acid solution. The two phases are separated, the aqueous phase is extracted with methylene chloride (3 x 30 mL), and the combined organic phases are washed with pH 7 aqueous phosphate buffer (4 x 80 mL) (Note 15), then dried with anhydrous sodium sulfate and concentrated under reduced pressure to give 7.89 g (99% crude yield) of the aldehyde **5** as a clear yellow oil (Notes 21 and 22). Analysis of crude aldehyde **5** by ^1H NMR indicates a chemical purity of $> 95\%$.

2. Notes

1. The glass components of the apparatus were dried overnight in a 150°C oven and allowed to cool in a desiccator over a drying agent before assembly.
2. Acetyl chloride was purchased from the Acros Chimica and distilled before use. The checkers purchased acetyl chloride from Aldrich Chemical Company, Inc., and used it without purification. *Caution! Acetyl chloride is a reactive substance that must be handled in a fume hood.*
3. Methanol was dried before use by distillation from magnesium methoxide under an atmosphere of nitrogen.
4. L-Serine was purchased from the Acros Chimica or Aldrich Chemical Company, Inc., and used without purification.
5. Di-tert-butyl dicarbonate was purchased from the Acros Chimica or Aldrich Chemical Company, Inc., and used without purification.

6. Tetrahydrofuran was dried before use by distillation from sodium metal and benzophenone under an atmosphere of nitrogen.

7. Triethylamine was purchased from the Acros Chimica or Aldrich Chemical Company, Inc., and used without purification.

8. Submitters report an optical rotation value for crude N-Boc-L-serine methyl ester **2** of $[\alpha]_D -19.1^\circ$ (MeOH, *c* 4.07), very close to that reported by McKillop, et al.² (lit.² $[\alpha]_D -18.9^\circ$ (MeOH, *c* 5.0)). Checkers report the following data for **2**: $[\alpha]_D^{23} 17.0^\circ$ (MeOH, *c* 4.41); ¹H NMR (300 MHz, CDCl₃) δ : 1.42 (s, 9 H), 3.03 (br s, 1 H), 3.75 (s, 3 H), 3.84 (dd, 1 H, *J* = 11, 3.3), 3.93 (br d, 1 H, *J* = 8.1), 4.33-4.36 (m, 1 H), 5.55 (br d, 1 H, *J* = 7.5); ¹³C NMR (75 MHz, CDCl₃) δ : 28.5, 52.7, 55.7, 63.3, 80.2, 155.6, 171.2; IR (neat) cm⁻¹: 3400, 1717. Anal. Calcd for C₉H₁₇NO₅: C, 49.31; H, 7.82; N, 6.39. Found C, 49.51; H, 7.86; N, 6.21.

9. Acetone was distilled from potassium permanganate prior to use.

10. 2,2-Dimethoxypropane and boron trifluoride etherate were purchased from Acros Chimica or Aldrich Chemical Company, Inc., and used without further purification.

11. TLC analysis on silica gel 60F-254 plates eluting with (1:1) cyclohexane-ethyl acetate showed the clean formation of ester **3** with *R_f* = 0.74 (visualized with 0.3% ninhydrin in (97:3) butanol-acetic acid) at the expense of starting material with *R_f* = 0.4. The sample of the oxazolidine ester was neutralized with a little triethylamine prior to TLC analysis.

12. Submitters report an optical rotation for the crude oxazolidine methyl ester **3** of $[\alpha]_D -54.4^\circ$ (CHCl₃, *c* 1.07), nearly identical to that found by McKillop, et al.² [lit.² $[\alpha]_D -54.0^\circ$ (CHCl₃, *c* 1.3)]. Purification with flash chromatography on silica gel eluting with (85:15) cyclohexane-ethyl acetate gave a product with a maximum rotation of $[\alpha]_D -58.3^\circ$ (CHCl₃, *c* 0.86), very close to that reported by Garner, et al.³ (lit.³ -57°). Checkers report the following data for **3**: $[\alpha]_D^{23} -53.5^\circ$ (CHCl₃, *c* 1.05); ¹H NMR (400

MHz, C₆D₆, 75°C) δ : 1.39 (s, 9 H), 1.54 (br s, 3 H), 1.82 (br s, 3 H), 3.34 (s, 3 H), 3.74 (m, 1 H), 3.80 (dd, 1 H, $J = 8.8, 3.2$), 4.26 (m, 1 H); ¹³C NMR (100 MHz, C₆D₆, 75°C) δ : 24.7, 25.3, 28.4, 51.6, 59.8, 66.4, 79.9, 95.5, 151.4, 171.3; IR (neat) cm⁻¹: 2980, 1759, 1708. Anal. Calcd for C₁₂H₂₁NO₅: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.52; H, 8.29; N, 5.44.

13. Lithium aluminum hydride was purchased from Acros Chimica or Aldrich Chemical Company, Inc., and used without further purification.

14. TLC analysis on silica gel plates eluting with (7:3) cyclohexane-ethyl acetate showed the clean formation of the alcohol with $R_f = 0.24$ (visualized with 0.3% ninhydrin in (97:3) butanol-acetic acid) at the expense of the starting material with $R_f = 0.55$.

15. Checkers used an aqueous NaH₂PO₄/Na₂HPO₄ buffer with a phosphate concentration of ca. 0.5 M.

16. Submitters found the optical rotation of the crude alcohol to be $[\alpha]_D -23.9^\circ$ (CHCl₃, c 1.0). Purification with flash chromatography on silica gel eluting with (7:3) cyclohexane-ethyl acetate gave a colorless syrup that solidified upon cold storage [mp 45-46°C; $[\alpha]_D -26.7^\circ$ (CHCl₃, c 1.0)], [lit.^{3a} mp 38-39°C; $[\alpha]_D -24.0^\circ$ (CHCl₃, c 1.61)]. Occasionally the compound crystallized at room temperature to give colorless prisms with a maximum mp of 49-51°C. Checkers report the following data for **4**: $[\alpha]_D^{23} -26.2^\circ$ (CHCl₃, c 0.79); ¹H NMR (400 MHz, C₆D₆, 70°C) δ : 1.37 (s, 9 H), 1.43 (br s, 3 H), 1.55 (br s, 3 H), 3.20 (br s, 1 H), 3.48 (m, 1 H), 3.63-3.68 (m, 3 H), 3.87 (m, 1 H); ¹³C NMR (100 MHz, C₆D₆, 70°C) δ : 24.3, 27.3, 28.4, 59.7, 64.0, 65.5, 80.1, 94.1, 153.4; IR (neat) cm⁻¹: 3430, 1699, 1380, 1260, 1174, 1050, 848. Anal. Calcd for C₁₁H₂₁NO₄: C, 57.12; H, 9.15; N, 6.00. Found: C, 56.84; H, 9.10; N, 6.06.

17. Methylene chloride was dried before use by distillation over calcium hydride under an atmosphere of nitrogen.

18. Dimethyl sulfoxide was purchased from Acros Chimica or Aldrich Chemical Company, Inc., and distilled under reduced pressure before use.

19. Oxalyl chloride was purchased from Acros Chimica or Aldrich Chemical Company, Inc., and distilled under an atmosphere of nitrogen before use. *Caution! Oxalyl chloride is a reactive substance that must be handled in a fume hood.*

20. N,N-Diisopropylethylamine was purchased from Acros Chimica and used without further purification.

21. The optical rotation of the crude aldehyde was $[\alpha]_D -89.7^\circ$ (CHCl_3 , c 1.65). Purification by flash chromatography on silica gel eluting with (4:1) cyclohexane-ethyl acetate gave a product with a rotation of $[\alpha]_D -95.5^\circ$ (CHCl_3 , c 0.78), (lit.³ $[\alpha]_D -105^\circ$). Checkers report the following data for **5**: $[\alpha]_D^{23} -93.3^\circ$ (CHCl_3 , c 1.10); ^1H NMR (400 MHz, C_6D_6 , 70°C) δ : 1.34 (s, 9 H), 1.40 (br s, 3 H), 1.58 (br s, 3 H), 3.57 (d, 1 H, $J = 7.6$), 3.67 (d, 1 H, $J = 7.6$), 3.91 (m, 1 H), 9.33 (br s, 1 H); ^{13}C NMR (100 MHz, C_6D_6 , 70°C) δ : 24.1, 26.0, 28.3, 63.7, 65.1, 80.6, 95.0, 151.8, 198.0; IR (neat) cm^{-1} : 1739, 1710. Anal. Calcd for $\text{C}_{11}\text{H}_{19}\text{NO}_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.59; H, 8.27; N, 5.91.

22. Enantiomeric purity was determined to be 96-98% by ^1H NMR analysis of the Mosher esters⁴ of the alcohols **4** and ent-**4** obtained by reduction of the aldehydes **5** and ent-**5**. To an ice-cold solution of aldehyde **5** (0.10 g, 0.44 mmol) in 5 mL of methanol was added solid sodium borohydride (33 mg, 0.88 mmol). After the mixture was stirred for 30 min at this temperature, the TLC in (7:3) cyclohexane-ethyl acetate showed the clean formation of the alcohol **4**. The mixture was treated with 0.05 mL of acetone and concentrated to dryness under reduced pressure. The residue was partitioned between water (10 mL) and ethyl acetate (10 mL) and the phases were separated. The aqueous phase was extracted with three 10-mL portions of ethyl acetate. The combined organic phases were dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash

chromatography on silica gel eluting with (7:3) cyclohexane-ethyl acetate to give 71 mg (70% yield) of pure alcohol **4** as a colorless oil: $[\alpha]_D -26.4^\circ$ (CHCl_3 , c 0.58). To a solution of the alcohol (50 mg, 0.22 mmol), N,N' -dicyclohexylcarbodiimide (54 mg, 0.26 mmol) and 4-dimethylaminopyridine (3.0 mg, 0.025 mmol) in dry methylene chloride (0.5 mL) was added a solution of (R)-(+)- α -methoxy- α -(trifluoromethyl)phenylacetic acid (61 mg, 0.26 mmol, Aldrich Chemical Company, Inc.) in 0.26 mL of dry methylene chloride. The mixture was stirred overnight (14 hr) at room temperature, filtered to remove N,N' -dicyclohexylurea, and partitioned between ethyl acetate (3 x 5 mL) and water (5 mL). The combined organic phases were washed with 5-mL each of 1 M hydrochloric acid, water, and saturated aqueous sodium bicarbonate solution, then dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel, eluting with (9:1) cyclohexane-ethyl acetate, to give 83 mg (84% yield) of product with the following properties: $[\alpha]_D +11.1^\circ$ (CHCl_3 , c 0.7); ^1H NMR (300 MHz, $\text{DMSO}-d_6$, 80°C) δ : 1.42 (s, 6 H), 1.44 (s, 9 H), 3.48 (s, 3 H), 3.69 (dd, 1 H, $J = 2.5, 9.4$), 3.96 (dd, 1 H, $J = 6.0, 9.4$), 4.01-4.11 (m, 1 H), 4.28 (dd, 1 H, $J = 7.5, 10.5$), 4.48 (dd, 1 H, $J = 3.3, 10.5$), 7.49 (s, 5 H). The same procedure was performed with ent-**5**. The resulting ester showed the following properties: $[\alpha]_D +53.6^\circ$ (CHCl_3 , c 0.68); ^1H NMR (300 MHz, $\text{DMSO}-d_6$, 80°C) δ : 1.37 (s, 3 H), 1.41 (s, 3 H), 1.43 (s, 9 H), 3.50 (s, 3 H), 3.73 (dd, 1 H, $J = 2.0, 9.4$), 3.98 (dd, 1 H, $J = 6.5, 9.4$), 4.04-4.14 (m, 1 H), 4.28 (dd, 1 H, $J = 7.3, 10.5$), 4.46 (dd, 1 H, $J = 3.1, 10.5$), 7.49 (s, 5 H).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Since the first appearance in the literature,⁵ the ingeniously protected serine-derived aldehyde **5** (Garner aldehyde) has attracted considerable attention as a model chiral α -amino carbonyl compound for stereochemical studies,⁶ and a precursor to interesting biologically active compounds such as amino sugars,⁷ aza sugars,⁸ sphingosines,⁹ and unusual amino acids.¹⁰ Compound **5** was designed⁵ to meet some essential requirements for wide application in synthesis. These include: (1) easy and large scale preparation, (2) configurational and chemical stability, (3) high stereoselectivity during addition reactions, (4) easy and selective removal of O- and N-protective groups. Almost all these features occur and greatly increased the numerous synthetic applications of aldehyde **5** over the years. Nevertheless the issue regarding feature (1) is worth reconsideration since it is crucial to the exploitation of the advantages associated with features (2)-(4). The aim of this work is to provide an improved preparation of **5**, partly along the lines of the previous procedures reported by Garner³ and McKillop² and their co-workers, partly by a new reaction sequence described by Roush and Hunt,^{7b} and by the submitters.¹¹

The original Garner preparation³ of **5** involves the conversion of serine into the protected methyl ester **3** and controlled reduction of the latter by DIBAL. The reaction sequence employed for the preparation of **3** involves the protection of the amino acid as N-Boc derivative using di-tert-butyl dicarbonate, esterification with methyl iodide or diazomethane, and acetonization with 2,2-dimethoxypropane under acid catalysis. The N-Boc methyl serinate and the ester **3** require purification by vacuum distillation or chromatography. In a modification to this procedure reported by McKillop,² the esterification reaction of serine is carried out first by methanol/acetyl chloride. The resulting ester is then converted into the N-Boc derivative **2** with di-tert-butyl dicarbonate and the latter transformed into **3** by acetonization. This procedure avoids

the use of methyl iodide or diazomethane and the toxic solvent benzene and gives ester **3** pure enough for the reduction by DIBAL according to the Garner procedure above. Roush^{7b} and the submitters¹¹ have observed that the DIBAL reduction of **3** leads to a mixture of the aldehyde **5**, primary alcohol **4**, and unreacted methyl ester **3** that were difficult to separate. Therefore it proved more convenient to obtain aldehyde **5** by a two-stage reduction-oxidation sequence. Thus, Roush^{7b} reported the reduction of **3** to the protected serinol **4** by the use of lithium aluminum hydride and Swern oxidation of the latter to **5** with DMSO/(COCl)₂ in the presence of triethylamine. While the chemical yield of **5** was quite good (85%) the enantiomeric purity was determined to be 86-87%, much lower than that reported by the Garner method (93-95%).

In our procedure methyl ester **3** is obtained by the McKillop method.² Conditions and yields of steps A and B are essentially identical to those reported by McKillop. The reduction of crude **3** with lithium aluminum hydride (step C) to the alcohol **4** was essentially quantitative. Also this isolated compound did not require any purification for use in the next oxidation step (D). This was carried out by the Swern oxidation method¹² using DMSO and (COCl)₂ in the presence of a base. This crucial operation where Roush obtained considerable racemization of the resulting amino aldehyde **5**, was carried out in the presence of diisopropylethylamine¹³ (Hünig's base). This simple yet important modification provided **5** in good yield (79-85% from **1**) and enantiomeric purity (96-98%) comparable to that reported by Garner.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N-[(1,1-Dimethylethoxy)carbonyl]-L-serine methyl ester: L-Serine,

N-[(1,1-dimethylethoxy)carbonyl]-, methyl ester (9); (2766-43-0)

Acetyl chloride (8,9); (75-36-5)

L-Serine (8,9); (56-45-1)

Di-tert-butyl dicarbonate: Formic acid, oxydi-, di-tert-butyl ester (8); Dicarboxylic acid, bis(1,1-dimethylethyl) ester (9); (24424-99-5)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

3-(1,1-Dimethylethyl) 4-methyl (S)-2,2-dimethyl-3,4-oxazolidinedicarboxylate:

3,4-Oxazolidinedicarboxylic acid, 2,2-dimethyl-, 3-(1,1-dimethylethyl) 4-methyl ester, (S)- (12); (108149-60-6)

2,2-Dimethoxypropane: Acetone, dimethyl acetal (8); Propane, 2,2-dimethoxy- (9); (77-76-9)

Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (1:1) (8); Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1) (9); (109-63-7)

N-[(1,1-Dimethylethoxy)carbonyl]-N,O-isopropylidene-L-serinol:

3-Oxazolidinecarboxylic acid, 4-(hydroxymethyl)-2,2-dimethyl-, 1,1-dimethylethyl ester (R)- (12); (108149-63-9)

Lithium aluminum hydride: Aluminate (1-), tetrahydro-, lithium (8); Aluminate (1-), tetrahydro-, lithium (I-4)- (9); (16853-85-3)

1,1-Dimethylethyl (S)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate:

3-Oxazolidinecarboxylic acid, 4-formyl-2,2-dimethyl-, 1,1-dimethylethyl ester, (S)- (11); (102308-32-7)

Dimethyl sulfoxide: Methyl sulfoxide (8); Methane, sulfinylbis- (9); (67-68-5)

Oxalyl chloride: HIGHLY TOXIC (8); Ethanedioyl dichloride (9); (79-37-8)

N,N-Diisopropylamine: Triethylamine, 1,1'-dimethyl- (8); 2-Propanamine, N-ethyl-N-(1-methylethyl)- (9); (7087-68-5)

Sodium borohydride: Borate (1-), tetrahydro-, sodium (8,9); (16940-66-2)

Dicyclohexylcarbodiimide: HIGHLY TOXIC: Carbodiimide, dicyclohexyl- (8);

Cyclohexanamine, N,N'-methanetetraylbis- (9); (538-75-0)

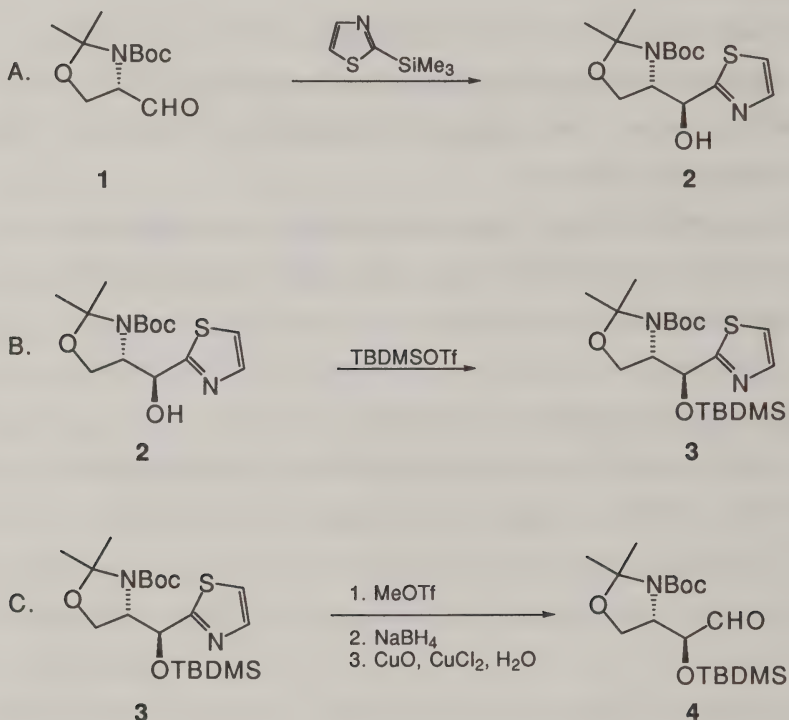
4-Dimethylaminopyridine: HIGHLY TOXIC: Pyridine, 4-(dimethylamino)- (8);

4-Pyridinamine, N,N-dimethyl- (9); (1122-58-3)

(R)-(+)- α -Methoxy- α -(trifluoromethyl)phenylacetic acid: Hydratropic acid, β,β,β -trifluoro- α -methoxy-, (+)- (9); (20445-31-2)

DIASTEREOSELECTIVE SYNTHESIS OF PROTECTED VICINAL AMINO ALCOHOLS: (S)-2-[(4S)-N-tert-BUTOXYCARBONYL-2,2-DIMETHYL-1,3-OXAZOLIDINYL]-2-tert-BUTYLDIMETHYLSILOXYETHANAL FROM A SERINE-DERIVED ALDEHYDE

(3-Oxazolidinecarboxylic acid, 4-[1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-oxoethyl]-2,2-dimethyl-, 1,1-dimethylethyl ester, [S-(R*,R*)]-)



Submitted by Alessandro Dondoni and Daniela Perrone.¹

Checked by Hou Chen and William R. Roush.

1. Procedure

A. (*S*)-2-[[*(4S)*]-*N*-*tert*-Butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]hydroxymethyl]-1,3-thiazole (**2**). A 100-mL, two-necked, round-bottomed flask, containing a magnetic stirring bar, is equipped with a low-temperature thermometer and one equalizing dropping funnel (Note 1). The funnel is charged with a solution of 2-(trimethylsilyl)thiazole (2-TST, 6.17 g, 39.2 mmol, Note 2) in 10 mL of methylene chloride (Note 3) and connected to a nitrogen flow line. The flask is charged with a solution of aldehyde **1** (7.5 g, 32.7 mmol, Note 4) in 65 mL of methylene chloride, then cooled to -35°C in a CryoCool bath and 2-TST is added dropwise over 15 min (Note 5). After completion of the addition, the funnel is washed with two 1-mL portions of methylene chloride, then replaced with a rubber septum. The flask is allowed to stand at -20°C (freezer) overnight (15 hr, Note 6), then allowed to warm to room temperature and concentrated under reduced pressure. To the residue dissolved in 40 mL of tetrahydrofuran is added, in one portion, tetrabutylammonium fluoride trihydrate (12.3 g, 39.0 mmol), and the brown reaction mixture is stirred at room temperature for 30 min (Notes 7 and 8). The solvent is removed under reduced pressure and the residue is partitioned between ethyl acetate (200 mL) and aqueous saturated sodium bicarbonate solution (2 x 250 mL). The aqueous phase is extracted with ethyl acetate (3 x 80 mL); then the combined organic phases are dried with anhydrous sodium sulfate and concentrated under reduced pressure using a 1-L flask to give 9.76 g (95% crude yield) of a clear brown solid. Analysis of crude product by ¹H NMR indicates a chemical purity of 90-95% and a diastereomeric ratio of 92% (anti-adduct). To the same 1-L flask equipped with a reflux condenser is added 475 mL of cyclohexane. The mixture is warmed at 80°C (water bath) until an homogeneous solution is obtained (Note 9). The hot solution is quickly filtered and allowed to cool to room temperature and to stand at this temperature overnight, at which time a white

precipitate is formed. The precipitate is collected by filtration and washed with three 10-mL portions of cold cyclohexane to give 7.15-7.50 g (70-73% yield) of **2** as a white solid: mp 171-173°C (Note 10). The filtrate is concentrated under reduced pressure and purified by flash chromatography with a 5 x 14-cm column of silica gel (Note 11), (cyclohexane-ethyl acetate (2:3) and 0.2% of triethylamine), to give an additional 1.20-1.40 g (11.6-13.6% yield) of a mixture of syn- and anti- (**2**) adducts (Note 12). Analysis of this mixture by ¹H NMR indicates a syn/anti diastereomeric ratio of 1.2:1.

B. (S)-2-[[[(4S)-N-tert-Butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]-tert-butyldimethylsiloxy]-1,3-thiazole (3). A 100-mL, one-necked, round-bottomed flask (Note 1) equipped with a magnetic stirring bar and a rubber septum is charged with a solution of the alcohol **2** (4.0 g, 12.7 mmol), 99% triethylamine (3.54 mL, 25.5 mmol), and 4-dimethylaminopyridine (DMAP, 0.12 g, 0.98 mmol) in 30 mL of N,N-dimethylformamide (Notes 13 and 14). While the solution is stirred at room temperature, tert-butyldimethylsilyl trifluoromethanesulfonate (4.38 mL, 19.1 mmol, Note 15) is introduced into the reaction flask through the rubber septum using a syringe over a period of 1 min. *Caution! tert-Butyldimethylsilyl trifluoromethanesulfonate is a toxic compound that should be handled in a well-ventilated fume hood.* After stirring at room temperature for 1 hr (Note 16), 4 mL of methanol is added via syringe. The reaction solution is stirred for an additional 30 min, then the solvent is removed under reduced pressure. The residue is dissolved in 60 mL of hexanes-ethyl acetate (4:1) and washed with 100 mL of aqueous saturated sodium chloride (NaCl). The organic phase is dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 5.18-5.30 g (95-97% crude yield) of **3** as a colorless syrup (Note 17). Analysis of crude product by ¹H NMR indicates a chemical purity of > 98%.

C. (S)-2-[(4S)-N-tert-Butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]-2-tert-butylidimethylsiloxyethanal (**4**). A 100-mL, one-necked, round-bottomed flask, equipped with a 2-cm egg-shaped magnetic stirring bar (Note 18), is charged with a mixture of the O-silyl ether **3** (2.0 g, 4.66 mmol), activated 4 Å powdered molecular sieves (9.33 g), and 47 mL of acetonitrile (Notes 19 and 20). The suspension is stirred at room temperature for 10 min, then methyl triflate (0.63 mL, 5.6 mmol, Note 21) is added via syringe. *Caution! Methyl triflate is toxic and a suspected carcinogen that should be handled in a well-ventilated fume hood.* The mixture is vigorously stirred for 15 min and concentrated to dryness under reduced pressure (Note 22). To the residue suspended in 47 mL of 1:1 methanol/diethyl ether and cooled with an ice-water bath is added under vigorous stirring sodium borohydride (0.39 g, 10.3 mmol, Note 23). Upon completion of the addition, the flask is removed from the ice bath and the solution is stirred at room temperature for 15 min, diluted with acetone (4 mL) and filtered through a Celite pad. The pad is rinsed with three 47-mL portions of acetone and the filtrate is concentrated under reduced pressure (Note 24). The residue is dissolved in 47 mL of acetonitrile-water (10:1) and the flask is placed in an ultrasonic cleaning bath and treated with 98% copper(II) oxide (2.97 g, 37.3 mmol, Note 25) and then with 95% copper(II) chloride dihydrate (0.79 g, 4.63 mmol, Note 25). After 10 min, the mixture is filtered through a Celite pad that is rinsed with four 47-mL portions of acetonitrile. The filtrate is concentrated under reduced pressure (Note 24) to give a brown syrup. The brown residue is sonicated for 5 min each with five 47-mL portions of diethyl ether, in an ultrasonic cleaning bath. The liquid layer is pipetted and filtered through a 1 x 6.5-cm (h x d) Florisil (100-200 mesh) pad. The filtrate appears almost colorless and is concentrated under reduced pressure (Note 24), to give 1.4-1.52 g (80-87% crude yield) of crude aldehyde **4** as a clear yellow oil (Note 26). Analysis of the crude product by ¹H NMR indicates a chemical purity of 90-95%. Crude **4** can be purified by flash chromatography over a 4.5 x 15-cm column of Silica Gel 60 (Note 11)

eluting with cyclohexane-ethyl (9:1) acetate to give 1.3-1.4 g (75-80% yield) of pure aldehyde (Note 27).

2. Notes

1. The glass components of the apparatus were dried overnight in a 150°C oven and allowed to cool in a desiccator over a drying agent before assembly.

2. 2-(Trimethylsilyl)thiazole (2-TST) is prepared according to the *Organic Syntheses* procedure;² it is also commercially available (Acros Chimica or Aldrich Chemical Company, Inc.). The commercial product was purified by distillation prior to use.

3. Methylene chloride was dried before use by distillation from calcium hydride under an atmosphere of nitrogen.

4. The preparation of the N-Boc-L-serinal acetonide is described in the accompanying procedure, p. 64. The crude aldehyde was used without further purification.

5. During the addition the clear yellow solution became red-orange.

6. After standing for 15 hr at -20°C the reaction solution returned to clear yellow.

7. Tetrahydrofuran was dried before use by distillation from sodium metal and benzophenone under an atmosphere of nitrogen.

8. Tetrabutylammonium fluoride trihydrate was purchased from Acros Chimica and used without further purification.

9. The checkers found it necessary to heat the solution to reflux to dissolve the solid. The hot solution was filtered by pouring into a preheated glass funnel containing a plug of glass wool to remove insoluble materials.

10. The product exhibits the following properties: $[\alpha]_D$ -51.2° (CHCl_3 , c 1.7), IR (KBr) cm^{-1} : 3230, 1695, 1656; ^1H NMR (300 MHz, DMSO-d_6 , 120°C) δ : 1.38 (s, 9 H), 1.46 (s, 3 H), 1.56 (s, 3 H), 3.82 (dd, 1 H, $J = 9.0, 6.8$), 3.95 (dd, 1 H, $J = 9.0, 3.0$), 4.26 (ddd, 1 H, $J = 6.4, 4.1, 3.0$), 5.15 (dd, 1 H, $J = 5.5, 4.1$), 6.11 (d, 1 H, $J = 5.5$, ex D_2O), 7.55 (d, 1 H, $J = 3.0$), 7.71 (d, 1 H, $J = 3.0$); ^{13}C NMR (75 MHz, CDCl_3) δ : 24.5, 25.7, 28.2, 62.2, 64.4, 73.4, 81.5, 94.6, 119.0, 142.4, 154.5, 172.6; HRMS, calcd for $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 315.1378, found 315.1379 Purification with flash chromatography on silica gel eluting with (1:1) cyclohexane-ethyl acetate gave a product with a maximum rotation of $[\alpha]_D$ -54.1° (CHCl_3 , c 1.0) and a mp of $174\text{--}175^\circ\text{C}$.

11. Silica Gel 60 (230-400 mesh) was obtained from Merck & Company, Inc.

12. Recrystallization of this mixture from cyclohexane (70 mL) gave ca. 0.40 g of **2** (4%).

13. Triethylamine (99%) and 4-dimethylaminopyridine were purchased from Acros Chimica and used without further purification.

14. N,N -Dimethylformamide was purchased from Acros Chimica and dried over activated 4 Å molecular sieves (8-12 mesh, Acros) before use.

15. *tert*-Butyldimethylsilyl trifluoromethanesulfonate was purchased from Acros Chimica and used as received under an atmosphere of nitrogen.

16. TLC analysis on Silica Gel 60F-254 plates eluting with cyclohexane-ethyl acetate (7:3) showed the clean formation of product with $R_f = 0.69$, at the expense of the starting material with $R_f = 0.3$. If a small amount of starting material was still present at this time, more *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.22 mL, 0.95 mmol) and 0.2 mL of triethylamine were added and the reaction mixture was stirred for a further 30 min, at which time the TLC analysis generally showed the reaction to be complete.

17. The crude product exhibits the following properties: $[\alpha]_D$ -46° (CHCl_3 , c 0.65); IR (KBr) cm^{-1} 1705, 1685; ^1H NMR (300 MHz, DMSO-d_6 , 120°C) δ : -0.04 (s, 3

H), 0.10 (s, 3 H), 0.94 (s, 9 H), 1.41 (s, 9 H), 1.45 (s, 3 H), 1.60 (s, 3 H), 3.80 (dd, 1 H, $J = 8.9, 7.0$), 4.09 (dd, 1 H, $J = 8.9, 3.5$), 4.17 (dt, 1 H, $J = 7.0, 3.5$), 5.55 (d, 1 H, $J = 3.5$), 7.60 (d, 1 H, $J = 3.1$), 7.75 (d, 1 H, $J = 3.1$); HRMS, calcd for $C_{20}H_{37}N_2O_4SSi$ $[M+H]^+$ 429.2243, found 429.2229. Purification with flash chromatography on silica gel eluting with cyclohexane-ethyl (9:1) acetate gave a product with a maximum rotation of $[\alpha]_D -47.6^\circ$ ($CHCl_3$, c 0.60). Upon cold storage a chromatographed sample of **3** crystallized: mp 53-55°C.

18. For efficient stirring a powerful magnetic stirrer should be used.

19. Activated 4 Å molecular sieves (powder, < 5 micron) were purchased from Aldrich Chemical Company, Inc., and used as received.

20. Acetonitrile was purchased from Acros Chimica and dried over activated 4 Å molecular sieves (8-12 mesh, Acros) before use.

21. Methyl triflate was purchased from Aldrich Chemical Company, Inc., and used as received.

22. TLC analysis on Silica Gel 60F-254 plates eluting with cyclohexane-ethyl acetate (9:1) showed the formation of product with $R_f = 0$, at the expense of the starting material.

23. Sodium borohydride was purchased from Aldrich Chemical Company, Inc., and used without further purification.

24. Bath temperature should not exceed 40°C.

25. Copper(II) oxide and copper(II) chloride dihydrate were purchased from Acros Chimica and used without further purification. The checkers found that the yield of Step C was substantially reduced (64-65%) when an old bottle of CuO was used. Results identical to those reported by the submitters were obtained using a new bottle of this reagent.

26. The crude product exhibits the following properties: $[\alpha]_D -40.7^\circ$ ($CHCl_3$, c , 0.6); IR (neat) cm^{-1} : 1740, 1712, 1690; 1H NMR (300 MHz, DMSO- d_6 , 120°C) δ : 0.1

(s, 6 H), 0.95 (s, 9 H), 1.44 (s, 9 H), 1.49 (s, 3 H), 1.54 (s, 3 H), 3.88 (dd, 1 H, J = 9.0, 2.5), 3.95 (dd, 1 H, J = 9.0, 5.9), 4.07 (dt, 1 H, J = 6.0, 2.5), 4.26 (dd, 1 H, J = 6.0, 2.0), 9.55 (d, 1 H, J = 2.0); HRMS, calcd for C₁₈H₃₆NO₅Si [M+H]⁺ 374.2362, found 374.2357.

27. After flash chromatography the product showed a maximum rotation of [α]_D -45.7° (CHCl₃, c 0.7).

Waste Disposal Information

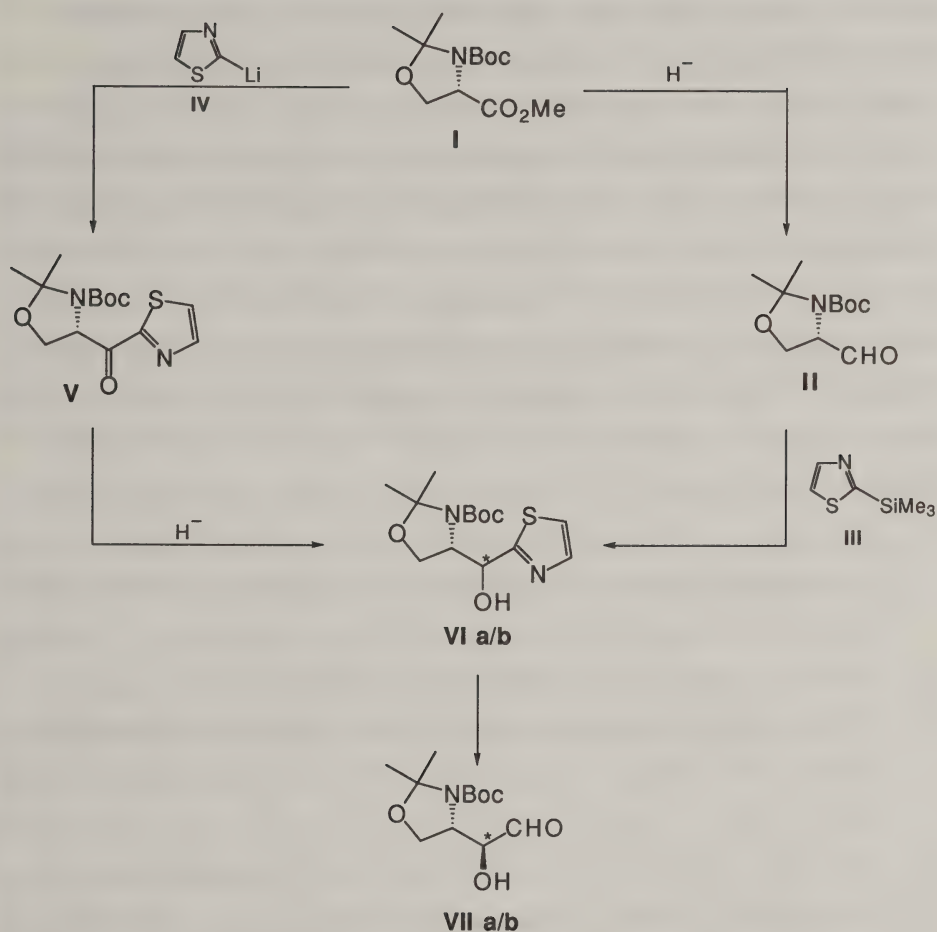
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academic Press; Washington, DC, 1995.

3. Discussion

The 2-amino-1,3-diol moiety is a structural unit featured by numerous natural products and synthetic analogues. For instance it is present at the polar head of sphingosines,³ and at the non-reducing end of aza sugars.⁴ Therefore chiral 3-amino-2,4-dihydroxybutanals are potential building blocks for the synthesis of those biologically active compounds.⁵ Since either R or S configuration at the stereocenters may be required, it is advisable to rely on a synthetic method that allows one to obtain these building blocks with all possible absolute and relative stereochemical arrangements. Accordingly, the submitters have approached the synthesis of these compounds by two routes (Scheme 1), which are both centered on the use of the thiazole ring as a convenient precursor of the formyl group (Thiazole Aldehyde Synthesis).⁶ These routes are complementary in the sense that starting from the same L-serine derived oxazolidine methyl ester **I** they lead to either R or S diastereomer oxazolidine alcohol **VI**. The S-configuration of the amino ester is employed for the

construction of the new stereocenter through internal asymmetric induction. Thus, in one route ester **I** is reduced to the oxazolidine aldehyde **II**, which then undergoes stereoselective anti-addition of the thiazole-bearing organosilane **III** to give the S-oxazolidine alcohol **Vla** as major product (aldehyde route).^{5a,7} In the other route the same ester **I** is first converted into the oxazolidine ketone **V** through nucleophilic substitution with another metalated thiazole **IV**. Ketone **V** is then reduced stereoselectively to give the R-oxazolidine alcohol **Vlb** as the major product (ketone route).^{5c,8} The opposite stereochemical outcome observed in this case is determined by the stereoselective hydride anti-addition to the carbonyl. The thiazole bearing diastereomeric oxazolidine alcohols **Vla** and **Vlb**, after suitable protection of the hydroxy group, are converted into the corresponding aldehydes **VIIa** and **VIIb** by the usual thiazole-to-formyl cleavage protocol.⁹ Evidently the antipodes of these aldehydes can also be prepared by the same routes starting from the D-serine derived enantiomer of ester **I**. Both routes can be scaled-up for the synthesis of gram quantities of these aldehydes. The thiazole ring serves as a convenient auxiliary in this methodology as well, since it tolerates different types of reaction conditions without any interference, and when needed it is readily converted into the formyl group. The thiazole-to-formyl cleavage occurs under mild and neutral conditions that do not affect the stereochemical integrity and chemical stability of the resulting aldehyde. Crude compound **VII** obtained by either the aldehyde or the ketone route is pure enough for use as a synthetic chiral building block.

Scheme 1



This procedure describes an example of the "aldehyde route". The addition of 2-(trimethylsilyl)thiazole (2-TST) to aldehydes occurs readily and does not require the presence of a fluoride ion source.¹⁰ The resulting secondary alcohol is as a rule isolated in very good yield. The sense of the diastereofacial selectivity of the addition reaction to chiral α -amino aldehydes can be controlled by differential protection of the

amino group. Specifically, compounds with double protection afford anti-amino alcohols, whereas those with single protection give syn-diastereomers.^{5a,7} Accordingly the addition of 2-TST to aldehyde **1** affords alcohol **2** as almost a single product (Step A). Rapid purification of this compound from the syn-isomer ($\leq 8\%$) is carried out by crystallization from cyclohexane. Pure alcohol **2** is then converted almost quantitatively into the tert-butyldimethylsilyl ether **3** (Step B). Other types of protection of the hydroxy group of **3** can also be applied. Finally crude O-silyl ether **3** is subjected to the conventional thiazole-to-formyl deblocking protocol⁹ (Step C) that is carried out through a sequence of very effective reactions, i.e., N-methylation, reduction, and metal-catalyzed hydrolysis. This aldehyde liberation requires no more than 4 hr of work. Isolated crude compound **4** is obtained in 52-59% yield from aldehyde **1**.

1. Dipartimento di Chimica, Laboratorio di Chimica Organica, Università, 44100 Ferrara, Italy.
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9. Dondoni, A.; Marra, A.; Perrone, D. *J. Org. Chem.* **1993**, *58*, 275.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-(Trimethylsilyl)thiazole: Thiazole, 2-(trimethylsilyl)- (10); (79265-30-8)
(S)-2-[[[(4S)-N-tert-Butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]hydroxymethyl]-
1,3-thiazole: 3-Oxazolidinecarboxylic acid, 4-(hydroxy-2-thiazolylmethyl)-2,2-
dimethyl-, 1,1-dimethylethyl ester, [(S-(R*,R*))]- (12); (115822-48-5)
1,1-Dimethylethyl (S)-4-formyl-2,2-dimethyloxazolidinecarboxylate:
3-Oxazolidinecarboxylic acid, 4-formyl-2,2-dimethyl-, 1,1-dimethylethyl ester,
(S)- (11); (102308-32-7)
Tetrabutylammonium fluoride trihydrate: Ammonium, tetrabutyl-, fluoride,
hydrate (8,9); (22206-57-1)
(S)-2-[[[(4S)-N-tert-Butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]-tert-butyl-
dimethylsiloxy]-1,3-thiazole: 3-Oxazolidinecarboxylic acid,
4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-thiazolylmethyl]2,2-dimethyl-,
1,1-dimethylethyl ester, [S-(R*,R*)]- (13) (168326-00-9)
Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)
4-Dimethylaminopyridine: HIGHLY TOXIC: Pyridine, 4-(dimethylamino)- (8);
4-Pyridinamine, N,N-dimethyl- (9); (1122-58-3)

N,N-Dimethylformamide: CANCER SUSPECT AGENT: Formamide, N,N-dimethyl- (8,9); (68-12-2)

tert-Butyldimethylsilyl trifluoromethanesulfonate: Methanesulfonic acid, trifluoro-, (1,1-dimethylethyl)dimethylsilyl ester (10); (69739-34-0)

(S)-2-2-[(4S)-N-tert-Butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]-2-tert-butyldimethylsiloxyethanal: 3-Oxazolidinecarboxylic acid, 4-[1-[(1,1-dimethylethyl)dimethylsilyloxy]-2-oxoethyl]-2,2-dimethyl-, 1,1-dimethylethyl ester, [S-(R*,R*)]- (13); (168326-01-0)

Acetonitrile (8,9); (75-05-8)

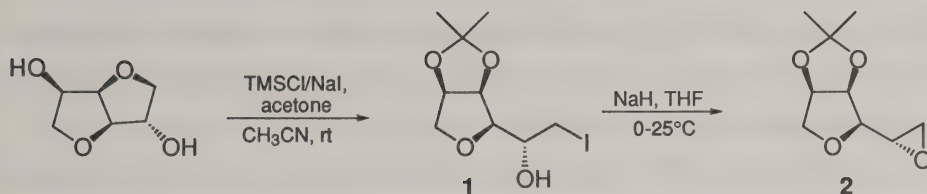
Methyl triflate: Methyl trifluoromethanesulfonate: Methanesulfonic acid, trifluoro-, methyl ester (8,9); (333-27-7)

Sodium borohydride: Borate (1-), tetrahydro-, sodium (8,9); (16940-66-2)

Copper(II) oxide: Copper oxide (8,9); (1317-38-0)

Copper(II) chloride dihydrate: Copper chloride dihydrate (8); Copper chloride, dihydrate (9); (10125-13-0)

**O⁴,O⁵-ISOPROPYLIDENE-1,2:3,6-DIANHYDRO-D-GLUCITOL
FROM ISOSORBIDE**



Submitted by S. Ejjiyar,¹ C. Saluzzo,² and R. Amouroux.²

Checked by Yuji Koga, Katsuya Uchiyama, and Koichi Narasaka.

1. Procedure

O⁴,O⁵-Isopropylidene-3,6-anhydro-1-deoxy-1-iodo-D-glucitol (1). A 1-L, two-necked, round-bottomed flask equipped with a reflux condenser connected to a mineral oil bubbler, a 100-mL, pressure-equalizing, dropping funnel capped with a rubber septum through which is inserted a nitrogen-inlet needle, and a magnetic stirring bar is charged with anhydrous sodium iodide (30.0 g, 0.200 mol) (Note 1), isosorbide (14.6 g, 0.100 mol) (Note 2), dry acetone (15 mL, 0.200 mol) (Note 3), and dry acetonitrile (350 mL) (Note 3). To this stirred mixture is added dropwise, at room temperature, through the dropping funnel, freshly distilled chlorotrimethylsilane (25.5 mL, 0.200 mol) (Note 4). After the addition is complete, the dropping funnel is rinsed with 10 mL of dry acetonitrile. The reaction mixture is stirred for 12 hr, with protection from light, at room temperature. To the resulting orange-brown mixture, ether (200 mL) and aqueous saturated sodium carbonate (60 mL) are added, and then the whole mixture is transferred to a 1-L separatory funnel and 100 mL of water is added. The aqueous phase is separated and extracted with two 100-mL portions of ether. The

combined organic layers are washed successively with 40 mL of an aqueous saturated sodium thiosulfate solution, 50 mL of an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate, and filtered. The solvent is removed with a rotary evaporator at 35°C. The resulting pale yellow oil solidifies on standing to afford 31.0 g (99%) of crude product **1** as a pale yellow solid (Note 5), which was used in the next step without further purification.

*O*⁴,*O*⁵-Isopropylidene-1,2:3,6-dianhydro-D-glucitol (**2**). An oven-dried, 500-mL, two-necked, round-bottomed flask is equipped with a magnetic stirring bar, a 250-mL, pressure-equalizing, dropping funnel, and a rubber septum with a needle connected to a dry nitrogen source. The nitrogen-flushed apparatus is charged with 100 mL of dry tetrahydrofuran (Note 6) and 2.8 g (0.117 mol) of sodium hydride (Note 7). The stirred suspension is cooled in an ice-water bath and a solution of 31 g (0.099 mol) of the crude iodo alcohol **1** in 150 mL of dry tetrahydrofuran is added dropwise through the dropping funnel during 1 hr. After the addition is complete, the dropping funnel is rinsed with 10 mL of tetrahydrofuran. After the mixture is stirred for 5 hr at room temperature, it is concentrated to a volume of about 100 mL under reduced pressure; then 150 mL of diethyl ether is added. The solution is re-cooled to 0°C and carefully quenched with 30 mL of an aqueous saturated solution of ammonium chloride. The whole mixture is poured into a 500-mL separatory funnel. After separation of the aqueous layer, the organic layer is washed twice with 20 mL of an aqueous saturated solution of sodium chloride. The combined aqueous layers, after addition of 50 mL of water, are extracted with two 50-mL portions of dichloromethane. The combined organic layers are dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 16.6 g of a light beige solid. Recrystallization from hexane (180 mL) gives 13.3 g of pure epoxide **2** as white needles (mp 77°C) (Note 8). The overall yield from isosorbide is 72%.

2. Notes

1. Sodium iodide was obtained from Acros Organics, a Fisher Scientific Company, and dried in a "drying pistol" under vacuum at 113°C in the presence of phosphorus pentoxide (P_2O_5).

2. Isosorbide (dianhydro-D-glucitol) was purchased from Fluka Chemical Corporation and was used without further purification. The checkers purchased isosorbide from Tokyo Chemical Industry Corporation.

3. Acetone (Purex analytical grade) and acetonitrile (HPLC grade) were purchased from SDS Company and used as received. The checkers purchased anhydrous acetone and acetonitrile from Kokusan Chemical Works and used them as received.

4. Chlorotrimethylsilane was obtained from Aldrich Chemical Company, Inc., and distilled from magnesium prior to use.

5. Physical properties and spectral data for **1** purified by recrystallization from petroleum ether (bp 40-60°C) are as follows: mp 72°C; $[\alpha]_D^{22}$ -66.6 (CH_2Cl_2 , c 1.0); IR (CH_2Cl_2) cm^{-1} : 3600, 3500, 2940, 2860, 1430, 1380, 1280, 1220, 1170, 1100, 1070, 1040, 980, 930, 900, 860, 840; 1H NMR ($CDCl_3$, 200 MHz) δ : 1.32 (s, 3 H), 1.48 (s, 3 H), 3.02 (d, 1 H, $J = 4.9$, OH), 3.4-3.6 (m, 4 H), 3.95 (dddd, 1 H, $J = 5.2, 5.2, 5.2, 4.9$), 4.17 (d, 1 H, $J = 10.8$), 4.72 (dd, 1 H, $J = 6.2, 3.6$), 4.82 (dd, 1 H, $J = 6.2, 3.6$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ : 9.4, 24.5, 25.9, 69.1, 72.5, 80.0, 81.2, 84.7, 112.4; MS (EI) m/e (rel. intensity): 299 (M -15, 17), 187 (M -127, 3), 171 (15), 144 (30), 127 (3), 86 (26), 69 (59), 59 (51), 57 (51), 55 (23), 44 (24), 43 (100). Anal. Calcd for $C_9H_{15}IO_4$: C, 34.41; H, 4.81; I, 40.40. Found: C, 34.55; H, 4.80; I, 40.27.

6. Tetrahydrofuran was predried over potassium hydroxide, then dried by distillation from sodium/benzophenone ketyl under nitrogen. The checkers purchased anhydrous tetrahydrofuran from Kanto Chemical Corporation and used it as received.

7. Sodium hydride was purchased from Aldrich Chemical Company, Inc., and used as received.

8. Physical properties and spectral data for **2** are as follows: white solid (mp: 77°C); $[\alpha]_D^{26}$ -80.5 (CH₃OH, *c* 0.502); IR (CH₂Cl₂) cm⁻¹: 3050, 2960, 2900, 2840, 1600, 1430, 1350, 1200, 1150, 1080, 1060, 1040, 1010, 970, 910, 880, 850; ¹H NMR (CDCl₃, 200 MHz) δ: 1.34 (s, 3 H), 1.53 (s, 3 H), 2.66 (dd, 1 H, *J* = 4.8, 2.7), 2.91 (dd, 1 H, *J* = 4.8, 4.4), 3.03 (dd, 1 H, *J* = 6.9, 3.7), 3.29 (ddd, 1 H, *J* = 6.9, 4.4, 2.7), 3.52 (dd, 1 H, *J* = 10.8, 3.6), 4.10 (d, 1 H, *J* = 10.8), 4.70 (dd, 1 H, *J* = 6.1, 3.7), 4.80 (dd, 1 H, *J* = 6.1, 3.6); ¹³C NMR (CDCl₃, 50 MHz) δ: 24.8, 26.0, 43.8, 50.0, 73.2, 81.2, 81.4, 84.6, 112.7; MS (EI) *m/e* (rel. intensity): 186 (*M*⁺, 0), 171 (*M*-15, 89), 149 (5), 111 (33), 69 (55), 68 (12), 59 (29), 57 (44), 55 (48), 43 (100), 41 (52), 39 (22), 29 (34). Anal. Calcd for C₉H₁₄O₄: C, 58.05; H, 7.58. Found: C, 57.83; H, 7.36.

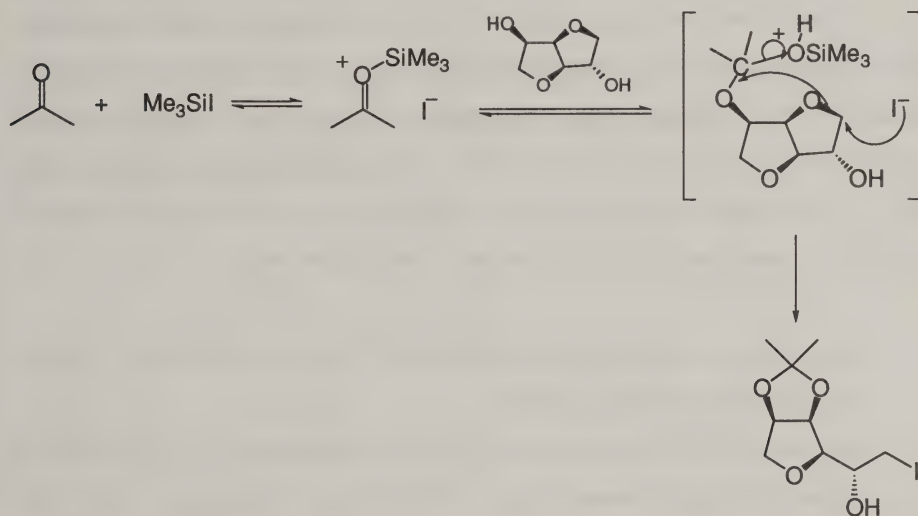
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

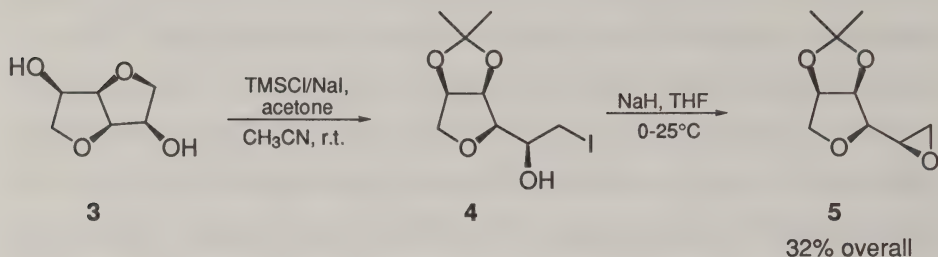
Isosorbide and isomannide are important by-products of the starch industry, arising from dehydration of D-sorbitol and D-mannitol. These commercial starting materials provide an easy and inexpensive access to optically pure functionalized tetrahydrofurans like O⁴,O⁵-isopropylidene-1-iodo-3,6-anhydro-1-deoxy-D-glucitol and O⁴,O⁵-isopropylidene-1-iodo-3,6-anhydro-1-deoxy-D-mannitol. This procedure describes a preparation of the former compound and the epoxide derived therefrom.

Ring opening of tetrahydrofuranic alcohols^{3,4} was previously described using iodotrimethylsilane in acetone, leading to iodo diols protected as their acetonide derivatives⁵. When isosorbide is treated with two equivalents of iodotrimethylsilane (TMSI/Nal) in acetonitrile, in the presence of two equivalents of acetone, only one of the two rings was cleaved. Although two different products may be expected from the scission of one of the two heterocycles of isosorbide, the reaction turned out to be regioselective. In fact the reaction is controlled by the acetonide formation, which requires that the two oxygen atoms be in a cis relationship. A plausible mechanism for the ring opening of isosorbide is illustrated below.



Basic treatment (NaH , THF) of the iodo alcohol from isosorbide gives the corresponding epoxide. This epoxide presents two advantages: first, it is more stable than the iodo alcohol on storage, and secondly, it offers a great potential for transformations.

Similar chemistry has been used to convert isomannide **3** into iodoalcohol **4** and epoxide **5**.³



To the submitters' knowledge, O⁴,O⁵-isopropylidene-1-iodo-3,6-anhydro-1-deoxy-D-glucitol and O⁴,O⁵-isopropylidene-1,2:3,6-dianhydro-D-glucitol have not been prepared before. However, the corresponding isomannide derivatives have been obtained in five steps from mannitol in low overall yield by Foster and Overend in 1951.^{6,7} The present method is a simple, rapid and inexpensive route to multigram amounts of these tetrahydrofuran derivatives in reasonable yields.

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2. Laboratoire de Chimie Organique Physique et Synthétique, CNRS, UMR 5622 Université Claude Bernard Lyon I, 43 Blvd du 11 Novembre 1918, 69622 Villeurbanne Cedex, France.
3. Ejjiyar, S.; Saluzzo, C.; Amouroux, R.; Massoui, M. *Tetrahedron Lett.* **1997**, *38*, 1575.
4. Amouroux, R.; Jatzcak, M.; Chastrette, M. *Bull. Soc. Chim. Fr.* **1987**, 505.
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6. Foster, A. B.; Overend, W. G. *J. Chem. Soc.* **1951**, 680.
7. Foster, A. B.; Overend, W. G. *J. Chem. Soc.* **1951**, 1132.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Isosorbide: Glucitol, 1,4:3,6-dianhydro- (8); D-Glucitol, 1,4:3,6-dianhydro-, (9);
(652-67-5)

Sodium iodide (8,9); (7681-82-5)

Acetonitrile: (8,9); (75-05-8)

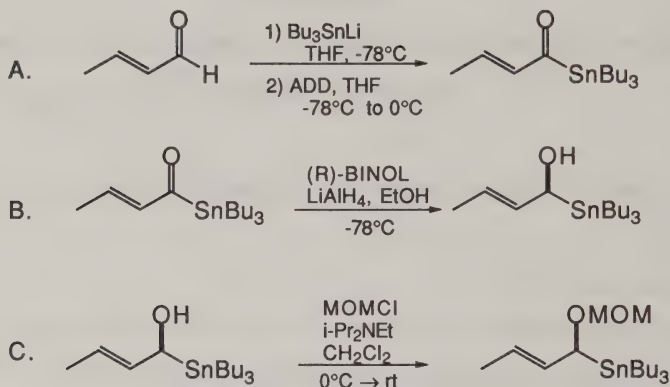
Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

Sodium thiosulfate: Thiosulfuric acid, disodium salt (8,9); (7772-98-7)

Sodium hydride (8,9); (7646-69-7)

SYNTHESIS OF (S,E)-1-(METHOXYMETHOXY)- 1-TRIBUTYLSTANNYL-2-BUTENE

(Stannane, tributyl[1-(methoxymethoxy)-2-butenyl]-, [S-(E)]-)



Submitted by James A. Marshall, Albert W. Garofalo, and Kevin W. Hinkle.¹

Checked by Peter Belica and Steven Wolff.

1. Procedure

Caution! Many organotin compounds are highly toxic. All operations should be conducted in an efficient fume hood. Gloves and appropriate eye protection should be worn while performing these experiments.

A. A 500-mL, one-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirring bar (Note 1), rubber septum and nitrogen inlet. The flask is charged with anhydrous tetrahydrofuran (THF) (150 mL) followed by diisopropylamine (4.60 mL, 32.8 mmol). The solution is stirred at 0°C and BuLi is added (2.5 M solution in hexane, 12.2 mL, 30.4 mmol). After 15 min, tributyltin hydride (7.70 mL, 27.8 mmol, Note 2) is added and the resulting yellow solution is stirred for 20 min. The solution is

cooled to -78°C by means of a dry ice-acetone bath and crotonaldehyde (2.10 mL, 25.3 mmol, Note 2) is added. After 30 min a solution of 1,1'-(azodicarbonyl)-dipiperidine (ADD) (8.31 g, 32.9 mmol, Note 2) in THF (65 mL) is added by means of a cannula. The resulting dark red reaction mixture is warmed to 0°C and stirred for 1 hr (Note 3). The reaction is then quenched with 100 mL of aqueous saturated ammonium chloride solution (Note 4) and extracted with two 100-mL portions of ether. The aqueous phase is saturated with sodium chloride and extracted with 100 mL of ether. The organic extracts are combined, dried over magnesium sulfate, filtered, and the solution is concentrated by rotary evaporation to a volume of 100 mL (Note 5). The orange solution is separated from a yellow precipitate by means of a cannula into a 2-L, two-necked, round-bottomed flask equipped with an overhead stirrer and containing 1 L of vigorously stirring hexane (Note 2) under a nitrogen atmosphere (Note 6). The resulting mixture is filtered through a glass-fritted funnel and the solvent is removed by rotary evaporation to afford the crude acyl stannane as a clear orange oil. This oil is dissolved in 65 mL of THF and immediately subjected to reduction with 2,2'-dihydroxy-1,1'-binaphthyl-lithium aluminum hydride (BINAL-H) (Part B).

Because of the lability of the acyl stannane it is important to have a freshly prepared solution of BINAL-H at -78°C ready for addition of the acyl stannane. This is best achieved by starting the following reduction procedure just prior to the acyl stannane sequence.

B. A 500-mL, two-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirring bar (Note 1), condenser, rubber septum and nitrogen inlet. The flask is charged with a suspension of lithium aluminum hydride (LiAlH_4) powder (2.13 g, 53.4 mmol) in 110 mL of anhydrous THF. The suspension is stirred at room temperature and a solution of ethanol (EtOH) (3.13 mL, 53.4 mmol, Note 7) in 10 mL of THF is added dropwise over a period of 15 min with vigorous evolution of hydrogen gas. The mixture is stirred for 20 min and a solution of (R)-1,1'-bi-2-naphthol (16.0 g,

55.8 mmol, Note 8) in 60 mL of THF is added over 1 hr by means of a cannula. The resulting cloudy, milky solution is refluxed for 2 hr (Note 9). The solution is cooled to -78°C in a dry ice-acetone bath and a solution of the acyl stannane in 65 mL of THF (Part A) is added over 45 min by means of a cannula. The reaction mixture is stirred for 16 hr (Note 10) as the bath slowly warms to room temperature. The reaction is quenched by the careful addition of 100 mL of aqueous saturated ammonium chloride solution and diluted with 100 mL of water and 200 mL of ether. The layers are separated and the aqueous layer is acidified by the addition of 200 mL of 1.0 M hydrochloric acid (HCl) and extracted with two 200-mL portions of ether. The organic layers are combined and washed with 200 mL of aqueous saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered and the solvent is removed by rotary evaporation. Hexane (100 mL) is added and distilled from the solution by rotary evaporation to ensure complete removal of residual ether and THF (Note 11). The solid yellow residue is triturated with 200 mL of hexane and filtered. Solvent is removed from the filtrate by rotary evaporation and the yellow oil is again triturated with 200 mL of hexane and filtered (Note 12). Solvent is again distilled from the filtrate by rotary evaporation to afford 8.97 g of crude hydroxy stannane as a yellow oil (Note 13).

While the α -hydroxy stannane is not as labile as the acyl stannane precursor, it should generally be converted to the ether derivative immediately after isolation.

C. The hydroxy stannane is dissolved in 100 mL of anhydrous methylene chloride in a 250-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar. The yellow solution is stirred at 0°C and diisopropylethylamine ($i\text{-Pr}_2\text{NEt}$) (8.80 mL, 50.5 mmol) is added, followed by chloromethyl methyl ether (2.90 mL, 38.2 mmol). After 5 hr the reaction is quenched with 100 mL of aqueous saturated ammonium chloride solution. The layers are separated and the aqueous layer is extracted with two 100-mL portions of ether. The

organic layers are combined, dried over magnesium sulfate, filtered, and the solvent is distilled by rotary evaporation. The residue is purified by column chromatography on silica gel (Note 14). Elution with hexane followed by EtOAc-hexane (1:9) affords 4.1-5 g (40-49% yield) of (S,E)-1-methoxymethyl-1-tributylstannyl-2-butene (Note 15).

2. Notes

1. All apparatus was dried by alternately evacuating the flask while heating with a flame and venting in dry nitrogen gas.

2. Tributyltin hydride, 97%, crotonaldehyde, 99%, 1,1'-(azodicarbonyl)-dipiperidine, 99%, and lithium aluminum hydride, 95%, were purchased from Aldrich Chemical Company, Inc. Hexane refers to a distilled, isomeric mixture of C₆H₁₄.

3. A viscous oil may form which makes stirring difficult. If this occurs, the flask is removed from the bath and shaken by hand until stirring can be resumed.

4. The reaction is monitored by TLC (silica gel; 1:9 EtOAc-hexane). The TLC plate is developed by dipping into a 0.02 M solution of phosphomolybdic acid in EtOH. The initially formed hydroxy stannane ($R_f = 0.52$) will stain blue without heating. The acyl stannane ($R_f = 0.69$) is observed by charring the plate.

5. Because of the air sensitive nature of the acyl stannane, the flask is vented with argon after removal of solvent.

6. A large volume of hexane is required to precipitate fully residual ADD and its reduction product. Alternatively the ether extracts may be concentrated to dryness and triturated with 250 mL of hexane.

7. The ethanol is distilled from calcium hydride and stored over molecular sieves.

8. Incomplete reduction of the acyl stannane is observed when fewer equivalents of BINAL-H are employed.

9. It was discovered by J. C. Saddler and co-workers at Upjohn that for reproducible results it was necessary to reflux the mixture of binaphthol, LiAlH_4 , and EtOH before performing the reduction. Enantioselective reduction of the acyl stannane can also be effected with Chirald, albeit with slightly diminished enantioselectivity.²

10. The reduction is generally complete within a few hours and may be monitored by TLC (Note 4). As stated in the procedure section, the submitters recommend that the hydroxy stannane not be stored after isolation. It can, however, be kept in the reaction mixture overnight.

11. The ensuing trituration is most efficient when residual ether and THF are completely removed.

12. Because of a slight solubility of the binaphthol in the crude hydroxy stannane mixture, two triturations are required. The binaphthol is recrystallized as previously described.³ Generally >90% of purified binaphthol is recovered.

13. The checkers found that the residue after removal of solvent contained water, which they removed azeotropically with toluene. Subsequent incomplete removal of the toluene led to amounts of stannane greater than theoretical.

14. The crude product was chromatographed on a silica gel column (ca. 150 g) using 300 mL of hexane followed by EtOAc-hexane (1:9 v/v) until complete elution. Because of a slight impurity, the early and late fractions of this separation were yellow; the middle fractions were colorless.

15. The following physical data were recorded: $[\alpha]_{\text{D}}^{25}$ -62.6 (CH_2Cl_2 , c 2.3), ^1H NMR (400 MHz, CDCl_3) δ : 0.90 (m, 15 H), 1.31 (m, 6 H), 1.50 (m, 6 H), 1.68 (d, 3 H, J = 6.2), 3.33 (s, 3 H), 4.56 (m, 1 H), 4.49, 4.67 (ABq, 2 H, J = 6.6), 5.39 (dq, 1 H, J = 15.4, 6.2), 5.58 (dd, 1 H, J = 15.4, 7.7); ^{13}C NMR (75 MHz, CDCl_3) δ : 8.9, 13.5, 17.5, 27.3, 29.0, 55.2, 72.4, 95.0, 119.9, 132.5. Anal. Calcd for $\text{C}_{18}\text{H}_{38}\text{O}_2\text{Sn}$: C, 53.35; H, 9.45. Found: C, 53.63; H, 9.28. The rotation corresponds to an enantiomeric excess of greater than 90% as previously reported.²

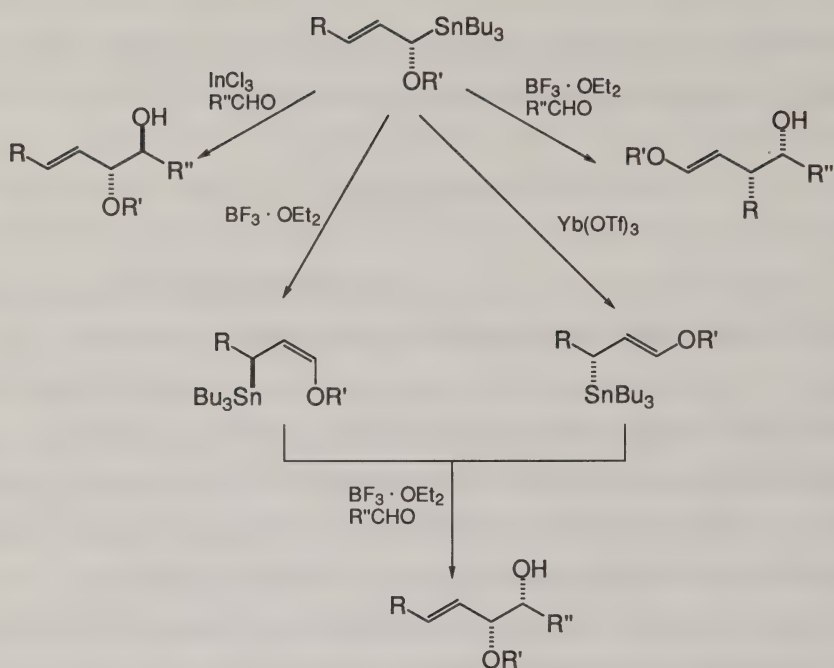
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academic Press; Washington, DC, 1995.

3. Discussion

Chiral α -alkoxyallylic stannanes [O-MOM, O-BOM (benzyloxymethyl)], as well as their α -siloxy (O-TBS) analogues, are useful reagents for chain homologation (Figure 1). The title compound has been used for the synthesis of carbohydrate homologues, cembranes, and macrolide precursors.^{4,5} The reagents are readily prepared and can be stored for extended periods with no apparent decomposition or racemization. The preparation of chiral α -siloxy allylic stannanes parallels the above procedure with the substitution of appropriate silylating agents in Part C. These stannanes undergo highly selective Lewis-acid promoted additions to aldehydes to give syn S_E' addition products.²

Figure 1



These reagents are also useful for the preparation of 1,2-diols. Upon exposure to Lewis acids such as boron trifluoride etherate ($\text{BF}_3 \cdot \text{OEt}_2$), the α -alkoxy and α -siloxy allyl stannanes undergo a stereospecific, intermolecular 1,3-isomerization to give γ -alkoxy- and γ -siloxy allylic stannanes.^{3,6,7} When tert-butyldimethylsilyl trifluoromethanesulfonate is substituted for chloromethyl methyl ether in the above procedure, the isomeric γ -siloxy allylic stannane can be obtained directly with no loss of enantioselectivity.⁶ These stannanes can then be added to various aldehydes to give monoprotected 1,2-diols with high diastereoselectivity.⁸

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6. Marshall, J. A.; Welmaker, G. S. *J. Org. Chem.* **1992**, *57*, 7158.
7. Isomerization of α -silyloxy and α -alkoxyallyl stannanes using either $\text{BF}_3 \cdot \text{OEt}_2$ or lithium perchlorate (LiClO_4) affords (Z)- γ -siloxy- and γ -alkoxyallylic stannanes. Treatment with $\text{Yb}(\text{OTf})_3$ affords mixtures of (Z)- and (E)- γ -siloxy- and γ -alkoxyallylic stannanes. See: Marshall, J. A.; Jablonowski, J. A.; Elliott, L. M. *J. Org. Chem.* **1995**, *60*, 2662.
8. While these reagents have largely been used to form syn-1,2-diols (see Refs. 3, 4, and 5), recently methodology has been developed that allows access to anti-1,2-diols with similar diastereoselectivity. See: Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1995**, *60*, 1920.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S,E)-1-(Methoxymethoxy)-1-tributylstannyl-2-butene: Stannane, tributyl[1-(methoxymethoxy)-2-butenyl]-, [S-(E)]- (12); (131433-64-2)

Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Tributyltin hydride: Stannane, tributyl- (8,9); (688-73-3)

Crotonaldehyde: Crotonaldehyde, (E)- (8); 2-Butenal, (E)- (9); (123-73-9)

1,1'-(Azodicarbonyl)dipiperidine [ADD]: Diimide, bis(piperidinocarbonyl)- (8);

Piperidine, 1,1'-(azodicarbonyl)bis- (9); (10465-81-3)

Lithium aluminum hydride: Aluminate(1-), tetrahydro-, lithium (8); Aluminate(1-), tetrahydro-, lithium, (T-4)- (9); (16853-85-3)

(R)-(+)-1,1'-Bi-2-naphthol: [1,1'-Binaphthalene]-2,2'-diol, (R)-(+)- (8);

[1,1'-Binaphthalene]-2,2'-diol, (R)- (9); (18531-94-7)

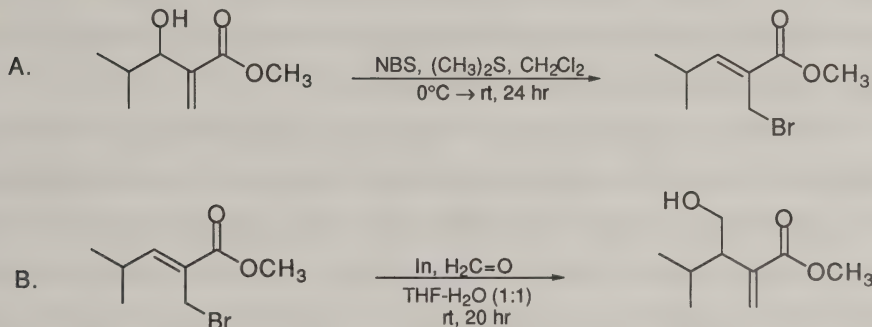
Phosphomolybdic acid: Molybdophosphoric acid ($\text{H}_3\text{PMo}_{12}\text{O}_{40}$), hydrate (9); (51429-74-4)

Chloromethyl methyl ether CANCER SUSPECT AGENT: Ether, chloromethyl methyl (8);

Methane, chloromethoxy- (9); (107-30-2)

Chirald: Benzenethanol, α -[2-(dimethylamino)-1-methylethyl]- α -phenyl-, [S-(R*,R*)]- (9); (38345-66-3)

**ALLYLINDATION IN AQUEOUS MEDIA: METHYL
3-(HYDROXYMETHYL)-4-METHYL-2-METHYLENEPENTANOATE**



Submitted by George D. Bennett and Leo A. Paquette.¹

Checked by Yan Dong and Steven Wolff.

1. Procedure

Caution! These reactions should be carried out in a fume hood because dimethyl sulfide is a stench compound, the bromo ester product is a lachrymator, and formaldehyde is a cancer suspect agent.

A. *Methyl Z-2-(bromomethyl)-4-methylpent-2-enoate.*² A dry, 250-mL, three-necked, round-bottomed flask fitted with an overhead stirrer and nitrogen inlet is charged with 100 mL of dichloromethane (CH_2Cl_2 , Note 1) and 25.9 g (0.15 mol) of N-bromosuccinimide (Note 2). The stirred suspension is cooled to 0°C and 9.29 g (0.15 mol) of dimethyl sulfide (Note 3) is added (Note 4), followed by 15.8 g (0.10 mol) of methyl 3-hydroxy-4-methyl-2-methylenepentanoate (Note 5). The resulting mixture is allowed to warm to room temperature, stirred for 24 hr, recooled to 0°C, diluted with 150 mL of pentane (Note 6), and poured into 200 mL of saturated brine and ice. The

separated aqueous phase is extracted with three 75-mL portions of pentane and the combined organic extracts are washed with 75 mL of brine, dried over magnesium sulfate (Note 7), gravity filtered, and concentrated on a rotary evaporator. The pale yellow residue is purified by column chromatography (Notes 8 and 9) to give 14.5 g (66%) of the bromo ester (Note 10) as a colorless oil.

B. Methyl 3-(hydroxymethyl)-4-methyl-2-methylenepentanoate. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar is charged with 11.0 g (0.05 mol) of methyl Z-2-(bromomethyl)-4-methylpent-2-enoate, 110 mL of tetrahydrofuran (Note 11), 110 mL of distilled water, 4.1 mL of a 37% w/w solution (0.05 mol) of aqueous formaldehyde (Note 12), and 6.32 g (0.06 mol) of indium powder (Note 13). The mixture is stirred vigorously at room temperature for 20 hr and diluted with 110 mL of ethyl acetate (Notes 14 and 15). The separated aqueous phase is extracted with three 75-mL portions of ethyl acetate and the combined organic extracts are washed with 75 mL of brine, dried over sodium sulfate (Na_2SO_4 , Note 16), gravity filtered, and concentrated on a rotary evaporator. The pale yellow residue is purified by column chromatography (Notes 8 and 17) to give 6.45 g (75%) (Note 18) of the hydroxy ester as a colorless oil (Note 19).

2. Notes

1. Dichloromethane was freshly distilled under nitrogen from calcium hydride.
2. N-Bromosuccinimide was used as purchased from the Aldrich Chemical Company, Inc.
3. Dimethyl sulfide was used as purchased from the Aldrich Chemical Company, Inc.

4. Dropwise addition via syringe successfully avoids such problems as rapid precipitation of the $\text{NBS} \cdot (\text{CH}_3)_2\text{S}$ complex, high exothermicity, and loss of stirring efficiency.

5. Methyl 3-hydroxy-4-methyl-2-methylenepentanoate³ was obtained by the means of a Baylis-Hillman reaction^{4,5} as follows. To a 500-mL, one-necked, round-bottomed flask equipped with a magnetic stir bar were added 82.3 g (1.14 mol) of isobutyraldehyde, 109.2 g (1.27 mol) of methyl acrylate, 7.28 g (0.057 mol) of 3-hydroxyquinuclidine, and 20 mL of chloroform (to predissolve the catalyst). The mixture was stirred at room temperature for 48 hr and concentrated to give the hydroxy ester (50.0 g, 28%) as a pale yellow oil. The product can be distilled (bp 83-87°C at 3 torr) or used in Part A without further purification. In the latter event, yields are 10-20% lower.

6. Reagent grade pentane was used as purchased from Fisher Scientific Company.

7. Anhydrous MgSO_4 was used as purchased from Fisher Scientific Company.

8. ICN (230-400 mesh) silica gel was purchased from Bodman Industries.

9. Silica gel (300 g) was packed to form a column of dimensions 19 cm x 6.5 cm. Elution was accomplished with hexanes:ethyl acetate (19:1), both of which were used as purchased from Mallinckrodt Inc. The flow rate was 4 drops/sec. After collection of 300 mL of eluant, 20-mL fractions were collected. The pure, UV-active product (10.0 g) eluted in fractions 34-48 ($R_f = 0.29$; silica gel developed with p-anisaldehyde). Fractions 13-33 and 49-57 were combined and concentrated to give 6.9 g of material which was purified by chromatography over 200 g of silica gel to afford an additional 4.5 g of pure bromide.

10. Spectral data were as follows: ^1H NMR (300 MHz, CDCl_3) δ : 1.09 (d, 6 H, $J = 6.6$), 2.71-2.83 (m, 1 H), 3.80 (s, 3 H), 4.23 (s, 2 H), 6.77 (d, 1 H, $J = 10.5$); ^{13}C NMR (75 MHz, CDCl_3) δ : 21.6, 24.2, 28.5, 52.1, 127.0, 154.4, 166.3; IR (CH_2Cl_2) cm^{-1} :

3035 (w), 2980 (s), 2886 (m), 1740 (s), 1648 (m), 1470 (s), 1370 (m), 715 (s); MS (EI, 70 eV): m/z ($M+OCH_3$) calcd 141.0915, obsd 141.0916 (100%).

11. THF was used as purchased from Mallinckrodt Inc.

12. Formaldehyde solution was used as purchased from EM Science.

13. Indium powder (99.99%) was used as purchased from the Aldrich Chemical Company, Inc.

14. If the aqueous phase is cloudy because of polymeric formaldehyde at this time, 1% hydrochloric acid can be added to clarify the solution.

15. Technical grade ethyl acetate was used as purchased from Mallinckrodt Inc.

16. Anhydrous Na_2SO_4 was used as purchased from Fisher Scientific Company.

17. Silica gel (275 g) was packed to form a column of dimensions 16 cm x 6.5 cm. Elution was accomplished with technical grade hexanes:ethyl acetate (7:3), both of which were used as purchased from Mallinckrodt Inc. The flow rate was 4 drops/sec. After collection of 150 mL of eluant, 20-mL fractions were collected. The UV-active product eluted in fractions 17-34 ($R_f = 0.30$; developed with I_2/SiO_2).

18. The submitters indicate that yields are 5-10% higher on smaller scale. The use of excess formaldehyde solution led to polymerization and lower yields of the desired product.

19. Spectral data are as follows: 1H NMR (300 MHz, $CDCl_3$) δ : 0.84 (d, 3 H, $J = 6.9$), 0.96 (d, 3 H, $J = 6.9$), 1.90 (m, 2 H), 2.45 (m, 1 H), 3.74 (dd, 1 H, $J = 7, 3$), 3.75 (s, 3 H), 3.77 (dd, 1 H, $J = 7, 3$), 5.60 (dd, 1 H, $J = 0.75, 1.1$), 6.29 (d, 1 H, $J = 1.2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ : 20.1, 20.5, 27.6, 50.5, 51.6, 62.7, 126.2, 140.8, 168.3; IR ($CHCl_3$) cm^{-1} : 3619 (m), 3444 (w), 2964 (s), 1714 (s), 1624 (m), 1440 (m), 1159 (m); MS (EI): m/e 173 (MH^+); Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.59; H, 9.57.

Waste Disposal Information

The malodorous aqueous phase from the work-up of reaction A was treated with commercial bleach before disposal. Metallic indium from reaction B was treated with concd HCl and diluted before disposal.

3. Discussion

This procedure exemplifies a general method⁶ for effecting carbon-carbon bond formation between a wide range of reactive halides and aldehydes or appropriately activated ketones⁷ in aqueous media. The properties of indium metal, most notably its first ionization potential (5.785 eV),⁸ inertness to dissolution in hot alkali⁹ and air oxidation,¹⁰ and low toxicity contribute well to smooth coupling of the derived allylindium reagents. The latter are slow to hydrolyze, amenable to chelation control under the proper circumstances,^{7,11} and conducive to long-range asymmetric induction.^{3,12} Significantly, indium(0) can easily be recovered from its salts by simple, conventional electrolysis.¹³

Indium-promoted organometallic reactions are greatly accelerated in water, especially when the coreactant carbonyl compound also has good water solubility. Otherwise, aqueous tetrahydrofuran can be used. To date, indium is the most effective metal for promoting Barbier-type reactions under aqueous conditions. As illustrated here, this is of particular value where formaldehyde is concerned, since the need to generate monomeric formaldehyde by thermal cracking is avoided.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Dimethyl sulfide: Methyl sulfide (8); Methane, thiobis- (9); (75-18-3)

Formaldehyde (8,9); (50-00-0)

Methyl Z-2-(bromomethyl)-4-methylpent-2-enoate: 2-Pentenoic acid,
2-(bromomethyl)-4-methyl-, methyl ester, (Z)- (12); (137104-39-3)

N-Bromosuccinimide: Succinimide, N-bromo- (8); 2,5-Pyrrolidinedione,
1-bromo- (9); (128-08-5)

Methyl 3-hydroxy-4-methyl-2-methylenepentanoate: Pentanoic acid, 3-hydroxy-4-
methyl-2-methylene-, methyl ester (10); (71385-30-1)

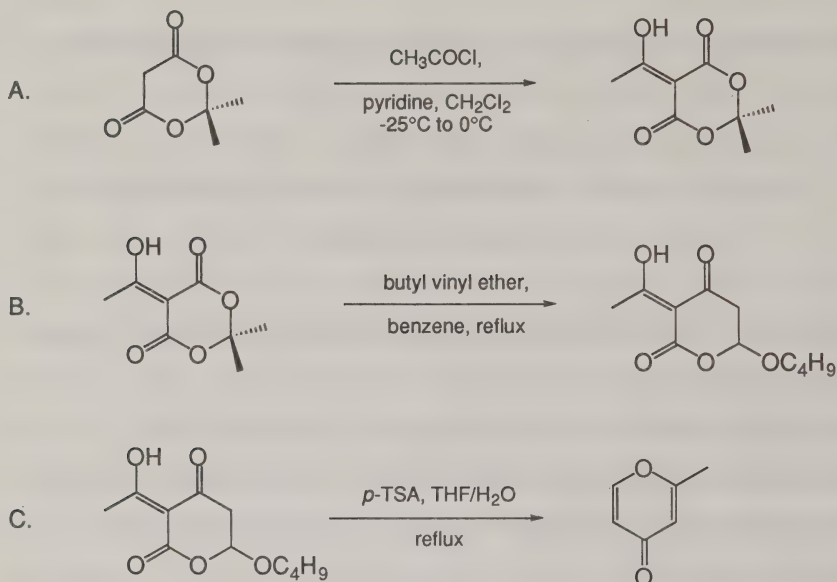
Indium (8,9); (7440-74-6)

Isobutyraldehyde (8); Propanal, 2-methyl- (9); (78-84-2)

Methyl acrylate: Acrylic acid, methyl ester (8); 2-Propenoic acid, methyl ester
(9); (96-33-3)

3-Hydroxyquinuclidine: 1-Azabicyclo[2.2.2]octan-3-ol (9); (1619-34-7)

THE SYNTHESIS OF 2-ALKYL-4-PYRONES FROM MELDRUM'S ACID



Submitted by Michael T. Crimmins, David G. Washburn, and Frank J. Zawacki.¹

Checked by Michelle Pacholec and Steven Wolff.

1. Procedure

A. *5-(1-Hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione*. A flame-dried, 500-mL, three-necked, round-bottomed flask is equipped with a stir bar, nitrogen inlet adapter, and a pressure-equalizing addition funnel fitted with a rubber septum. The flask is charged with 22.0 g of Meldrum's acid dissolved in 153 mL of methylene chloride, and 24.8 mL of pyridine (Note 1), and the mixture is cooled to -25°C (Note 2). A mixture of 18.3 mL of methylene chloride and 13.1 mL of acetyl chloride is slowly added to the reaction mixture via the addition funnel over 1 hr (Note 3). After the addition of the acetyl chloride is complete, the reaction is slowly warmed over 3 hr to

0°C. Methanol (30 mL) is added to quench the reaction and stirring is continued for 15 min. The reaction mixture is transferred to a 2000-mL separatory funnel, diluted with 100 mL of methylene chloride and washed with saturated aqueous ammonium chloride (3 x 140 mL) and 140 mL of water. The aqueous layers are combined and extracted with methylene chloride (3 x 100 mL). The combined organic layers are dried over 200 g of sodium sulfate for 3 hr (Note 4). The solution is filtered into a 1000-mL, round-bottomed flask and the methylene chloride is removed under reduced pressure. The residual orange solid can be purified by breaking up the solid into a fine powder with a mortar and pestle and placing it under vacuum overnight to remove any remaining pyridine to yield 26.0 g of acylated Meldrum's acid suitable for use in the next step (Note 5).

B. and C. 2-Methyl-4H-pyran-4-one. A 1000-mL, round-bottomed flask equipped with a stir bar and a reflux condenser is charged with the crude acylated Meldrum's acid, 80 mL of butyl vinyl ether and 287 mL of toluene (or benzene) (Note 6). The reaction mixture is heated to 80°C for 7 hr (Note 7). The volatile components are removed under reduced pressure to yield 31.81 g of product (Note 8). To the residue are added 765 mL of tetrahydrofuran, 191 mL of water and 2.7 g of p-toluenesulfonic acid. The mixture is heated to reflux for 18 hr, then the reaction is quenched with 10 g of solid sodium bicarbonate and allowed to stir for 15 min at 25°C (Note 9). The mixture is filtered to remove the sodium bicarbonate and the volatile components are removed under reduced pressure. The residue is dissolved in 500 mL of methylene chloride, placed in a separatory funnel and washed with 200 mL of water and 200 mL of brine solution. The aqueous layers are collected and extracted with methylene chloride (2 x 200 mL). The organic layers are combined, dried over 20 g of sodium sulfate for 1 hr, filtered into a 1000-mL, round-bottomed flask, and concentrated under reduced pressure. The resulting red oil is purified by chromatography using a 6-cm diameter glass column packed with 400 g of silica gel

(Note 10) with 2.5% methanol/methylene chloride as the eluant yielding 5.25-5.81 g (38.6-42.7%) of 2-methyl-4H-pyran-4-one (Note 11).

2. Notes

1. Meldrum's acid was purchased from Aldrich Chemical Company, Inc. Pyridine was distilled from calcium hydride. Methylene chloride was dried over alumina. The checkers found that recrystallization of Meldrum's acid from benzene was necessary in order to obtain reproducible yields of the acylated product.

2. A temperature of -25°C was reached through the use of a 29% calcium chloride - dry ice slurry.

3. Acetyl chloride was purchased from Aldrich Chemical Company, Inc., and was freshly distilled prior to use.

4. Alternatively, the addition of 5 g of magnesium sulfate ensures a dry product within 1 hr.

5. The product has an R_f of 0.22 in 5% methanol/methylene chloride (silica gel) and displays the following spectral data: ^1H NMR (300 MHz, CDCl_3) δ : 1.71 (s, 6 H), 2.64 (s, 3 H); ^{13}C (75 MHz, CDCl_3) δ : 37.5, 42.4, 45.1, 106.2, 118.6, 174.8, 184.2, 207.5. Checkers found this material to contain approximately 5% of Meldrum's acid. The acidic proton was not observed in the ^1H NMR spectrum.

6. Butyl vinyl ether was purchased from Aldrich Chemical Company, Inc., and was distilled from sodium under reduced pressure. Toluene was distilled from calcium hydride.

7. Reaction times vary depending on scale. For optimum results the consumption of the acylated Meldrum's acid is monitored by TLC.

8. The product has an R_f of 0.60 in 5% methanol/methylene chloride (silica gel) and can be purified with difficulty by column chromatography. The product had the

following spectral characteristics: ^1H NMR (300 MHz, CDCl_3) δ : 0.81 (t, 3 H, $J = 7$), 1.22 (dt, 2 H, $J = 7, 7$), 1.47 (m, 2 H), 2.53 (s, 3 H), 2.60 (dd, 1 H, $J = 17, 3$), 2.92 (dd, 1 H, $J = 17, 1.5$), 3.52 (m, 1 H), 3.83 (m, 1 H), 5.29 (dd, 1 H, $J = 3, 1.5$) ^{13}C (75 MHz, CDCl_3) δ : 27.5, 33.2, 40.3, 45.5, 52.7, 83.5, 101.1, 118.0, 176.8, 208.1, 214.0.

9. Solid sodium bicarbonate was added to reach a slightly basic ($\text{pH} = 7.5\text{-}8$) solution.

10. Silica gel was purchased from VWR Scientific.

11. The product is a red oil. The product has an R_f of 0.38 in 5% methanol/methylene chloride (silica gel) and shows the following spectral characteristics: IR (neat) cm^{-1} : 3007, 1665, 1615, 1410, 1385, 1340, 1250, 1215, 1170, 1055, 1005, 925, 890, 855, 820; ^1H NMR (250 MHz, CDCl_3) δ : 2.27 (d, 3 H, $J = 0.75$), 6.15 (d, 1 H, $J = 1.75$), 6.27 (dd, 1 H, $J = 6, 6$), 7.68 (d, 1 H, $J = 6$); ^{13}C (75 MHz, CDCl_3) δ : 18.7, 114.5, 115.5, 154.7, 165.6, 178.3.

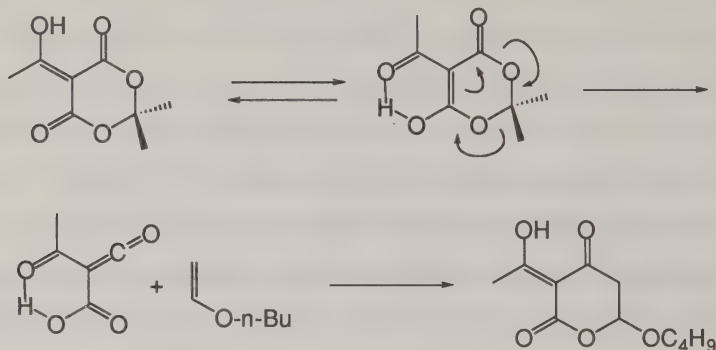
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

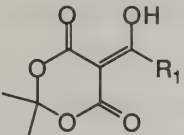
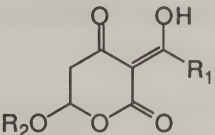
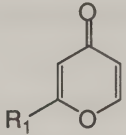
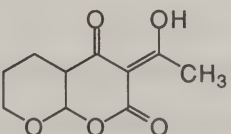
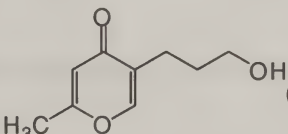
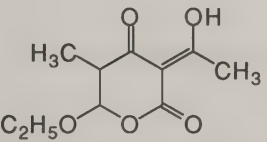
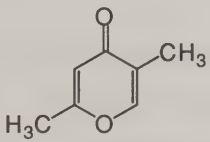
The procedure described here offers a general route to a variety of unsymmetrically substituted γ -pyrones from Meldrum's acid.² Substitution at the 2-position depends on the acid chloride chosen, while substitution at the 5-position is derived from the vinyl ether. A variety of substituted γ -pyrones have been synthesized by utilization of this method as illustrated in the Table. The intermediate pyrandione is believed to arise through the addition of the vinyl ether to an acyl ketene that results

from the thermal loss of acetone from the acylated Meldrum's acid.³ Treatment of the pyrandione with acid catalyzes decarboxylation and the loss of butanol to form the γ -pyrone.



Substituted γ -pyrones are versatile synthetic precursors. There is strong precedent for the metalation⁴ and bromination⁵ of the γ -position, which allows γ -pyrones to be used in alkylation and aldol reactions and makes them attractive intermediates in the synthesis of polyacetate and spiroketal containing natural products.⁶ They can also be used as cycloaddition substrates in the construction of complex polycyclic systems as West has demonstrated.⁷ Furthermore, γ -pyrones have been used by Wender in an oxidopyriliium-alkene cycloaddition, a key reaction in his synthesis of phorbol.⁸

Past methods used to synthesize γ -pyrones consist of the acylation of methoxybutyne⁹ or 4-methoxy-3-buten-2-one¹⁰ followed by acid-catalyzed hydrolysis and cyclization. Addition of ketenes to siloxydienes followed by acid-catalyzed elimination has also been employed.¹¹ The present method is superior to these procedures because of the greater diversity of substituted γ -pyrones that can be constructed, and because of the fact that the previous methods demand the use of strong base and low temperatures that make them less suited for scale up.

TABLE			
Acylated Meldrum's Acid	Pyrandione	Pyrone	(Yield)
			
$R_1 = \text{CH}_3$	$R_2 = \text{tert-C}_4\text{H}_9$	$R_1 = \text{CH}_3$	(61)
$R_1 = \text{C}_2\text{H}_5$	$R_2 = \text{C}_4\text{H}_9$	$R_1 = \text{C}_2\text{H}_5$	(75)
$R_1 = (\text{CH}_3)_2\text{CH}$	$R_2 = \text{C}_4\text{H}_9$	$R_1 = (\text{CH}_3)_2\text{CH}$	(57)
$R_1 = \text{C}_6\text{H}_5\text{CH}_2$	$R_2 = \text{C}_4\text{H}_9$	$R_1 = \text{C}_6\text{H}_5\text{CH}_2$	(85)
$R_1 = \text{CH}_3$			(53)
$R_1 = \text{CH}_3$			(40)

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Meldrum's acid: Malonic acid, cyclic isopropylidene ester (8); 1,3-Dioxane-4,6-dione,
2,2-dimethyl- (9); (2033-24-1)

Pyridine (8,9); (110-86-1)

Acetyl chloride (8,9); (75-36-5)

Acetylated Meldrum's acid: 1,3-Dioxane-4,6-dione, 5-(1-hydroxyethylidene)-2,2-
dimethyl- (11); (85920-63-4)

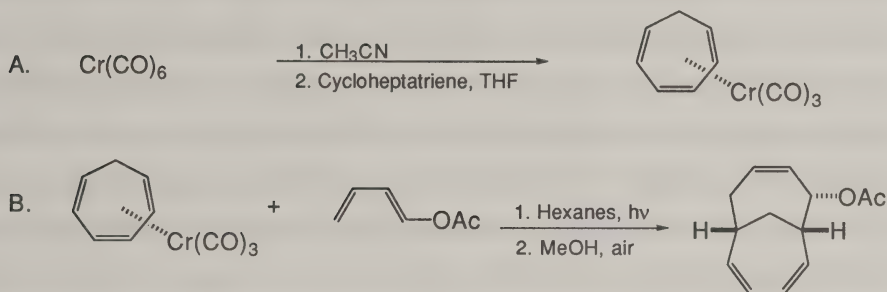
Butyl vinyl ether: Butane, 1-(ethenyloxy)- (9); (111-34-2)

3-Acetyl-6-butoxy-2H-pyran-2,4(3H)-dione: 2H-Pyran-2,4(3H)-dione,
6-butoxydihydro-3-(1-hydroxyethylidene)- (13); (182616-30-4)

p-Toluenesulfonic acid monohydrate (8); Benzenesulfonic acid,
4-methyl-, monohydrate (9); (6192-52-5)

2-Methyl-4-pyrone: 4H-Pyran-4-one, 2-methyl- (8,9); (5848-33-9)

**7 α -ACETOXY-(1H β , 6H β)-BICYCLO[4.4.1]UNDECA-2,4,8-TRIENE VIA
CHROMIUM-MEDIATED HIGHER ORDER CYCLOADDITION
(Bicyclo[4.4.1]undeca-3,7,9-triene-2-ol, acetate, endo- (\pm)-)**



Submitted by James H. Rigby¹ and Kevin R. Fales.

Checked by Robert E. Lee Trout and Amos B. Smith, III.

1. Procedure

A. *Tricarbonyl(η^6 -cycloheptatriene)chromium(0)*. An oven-dried complexation flask (Figure 1), fitted with an additional condenser (Note 1) and gas adapter, is charged with acetonitrile (300 mL). The solvent is heated to $\sim 40^\circ\text{C}$ under argon (Ar) (Note 2), chromium hexacarbonyl is added (45 g, 0.2 mol) (Note 3), and the mixture is immediately heated to reflux for 24 hr (Note 4). Toward the end of this time period (i.e., after ~ 20 hr), the cooling jacket attached to the flask is alternately filled with water and emptied to allow for complete digestion of the starting material. After complete conversion of the chromium hexacarbonyl is evident, the free condenser is quickly changed to a 9"-Vigreux column connected through an acetone/solid carbon dioxide (CO_2) condenser to a vacuum/argon line using a Firestone valve (Note 5). Vacuum (~ 0.1 mm) is quickly and cautiously applied to the system while simultaneously

removing the heating source (Note 6). The reaction mixture is evaporated to complete dryness by warming the reaction flask with a warm water bath as necessary (Note 7). The system is filled with argon and a previously prepared solution of cycloheptatriene (1.5 eq., 0.31 mol, 28.3 g, 32 mL) in tetrahydrofuran (THF) (50 mL) is added via syringe to the dry, bright yellow, solid tris(acetonitrile)chromium tricarbonyl intermediate. This addition is best performed under a very strong flow of argon through the top joint of the reaction apparatus. An additional 100 mL of THF is added to the mixture and the resulting solution is heated to reflux. After 48 hr, additional cycloheptatriene (1.0 eq., 0.2 mol, 20.5 g, 23 mL) is added and the reaction is continued until complete digestion of the $(\text{CH}_3\text{CN})_3\text{Cr}(\text{CO})_3$ intermediate is evident (Note 8). Solvent is removed under reduced pressure (Note 9), and the residue is dissolved in a mixture of hexanes (225 mL) and methylene chloride (225 mL). Celite (5.0 g) is added to the solution and the mixture is filtered through a Celite pad (5.5 cm x 1.0 cm). The filter cake is washed with methylene chloride (2 x 50 mL) and the filtrate is concentrated under reduced pressure to provide an oily red solid. After the solids are dried briefly under vacuum (~2 hr, 0.1 mm), they are triturated with chilled hexanes (100 mL), and the chilled solids are collected via vacuum filtration and washed with chilled hexanes (50 mL). The solids are dried under vacuum (0.1 mm) to yield the dark red tricarbonyl(η^6 -cycloheptatriene)chromium(0) (34.4-39.9 g, 75-85%, Note 10).

B. 7 α -Acetoxy-(1H β , 6H β)-bicyclo[4.4.1]undeca-2,4,8-triene. To a large, fully assembled photochemical reaction vessel (Figure 2) are added tricarbonyl(η^6 -cycloheptatriene)chromium(0) (10.0 g, 0.044 mol) and hexanes (4 L, Note 11). While the mixture is stirred it is purged with argon for 20-30 min and then 1-acetoxy-1,3-butadiene (1.5 eq., 7.4 g, 7.8 mL, 0.66 mol) is added via syringe (Note 12). The solution is irradiated (Note 13) using a Hanovia medium pressure 450W mercury vapor lamp (Note 14) for 6 hr or longer (Note 15) until complete digestion of the starting chromium complex is noted by TLC (Note 16). The reaction mixture is

transferred, portionwise, to a 2-L, round-bottomed flask using diethyl ether, and the solvents are removed under reduced pressure (Note 9). The residue is taken up in methanol (300 mL), with scraping as necessary, and the resultant slurry is stirred open to the atmosphere overnight. At this time, flash grade silica gel (10.0 g, Merck 230-400 mesh) is added to the green slurry and stirring is continued as necessary for complete decomplexation of the intermediate cycloadduct complex, as noted by TLC (Note 16). The reaction mixture is filtered through a Celite pad (9 cm diameter by ~1 cm deep), using additional methanol (3 x 50 mL) to rinse the flask and filter cake until the filtrate runs clear (Note 17). Solvent is removed under reduced pressure and the residue is dried overnight under ~0.1 mm vacuum to remove additional traces of solvent and unreacted diene (Note 18). The product is purified via flash column chromatography (Note 19) to yield ~98% pure (Note 20), 7 α -acetoxy-(1H β , 6H β)-bicyclo[4.4.1]undeca-2,4,8-triene (7.7 g, 86%) (Note 21) as a white solid (mp 54-57°C).

2. Notes

1. It is most convenient to attach cooling water in series to the free condenser first and then to the cooling jacket on the complexation flask.

2. The submitters used nitrogen at this point, but the checkers found that argon worked as well. The checkers also recommend the use of an Oxiclear gas purifier.

3. Fresh reagent grade acetonitrile was purchased from Fisher Scientific Co. and used without additional purification. Chromium hexacarbonyl was purchased from Strem Chemical Co. Celite and cycloheptatriene (90% technical grade) were purchased from Aldrich Chemical Company, Inc., and used without purification. THF was distilled from sodium/benzophenone ketyl.

4. Once heating of the reaction is begun, any significant cooling or exposure to the atmosphere generally causes degradation of the tris(acetonitrile)chromium

tricarbonyl intermediate. The reaction initially turns greenish yellow, but then quickly forms a bright yellow to golden color that becomes dark green upon degradation. Greenish, partially degraded intermediates can be carried through the sequence with a corresponding reduction in yield. The total time of reflux ranged from 24-26 hr.

5. This item may be purchased from Ace Glass Inc., Vineland, N.J., catalog #8766-12.

6. Vacuum must be applied carefully to avoid bumping, but must also be applied quickly and steadily to avoid degradation of the reaction intermediate.

7. *Warning!* Tris(acetonitrile)chromium tricarbonyl is highly pyrophoric and degrades rapidly when exposed to oxygen, but is reasonably stable in THF solution. Best yields are obtained when this intermediate is as free of acetonitrile as possible while avoiding formation of the green colored [Cr(III)] decomposition product, which develops on contact with air.

8. The reaction is monitored by TLC (silica gel, 6:1 hexanes: ethyl acetate). Typical characteristics are $R_f = 0.15$, a yellow spot [tris(acetonitrile)chromium tricarbonyl intermediate], and $R_f = 0.51$, a red spot (product complex). Total reaction time averaged ~180 hr.

9. Solvent is removed via rotary evaporator.

10. This product was typically found to be $\geq 98\%$ pure based on ^1H NMR analysis, and it may be used without further purification. However, the compound may be recrystallized from hexanes if necessary. The complex exhibits the following characteristics: TLC: $R_f = 0.51$ (silica gel, 6:1 hexanes:ethyl acetate); ^1H NMR (500 MHz, CD_2Cl_2) δ : 1.74 (d, 1 H), 2.95 (dt, 1 H, $J = 9.0, 14.0$), 3.40 (t, 2 H, $J = 7.5$), 4.87 (bs, 2 H), 6.09 (bs, 2 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ : 23.9 (CH_2), 57.1 (CH), 98.4 (CH), 101.1 (CH); IR (CDCl_3) cm^{-1} : 3052, 2895, 2848, 1982, 1974, 1917, 1897, 1886, 1877; HRMS calcd for $\text{C}_{10}\text{H}_8\text{CrO}_3$: m/e 227.9879, found 227.9881; LRMS [EI] (rel. %): 227.9 (19), 199.9 (13), 172.0 (15), 144.0 (74).

11. Performing this reaction at higher concentrations (i.e., in 1-2 L solvent) results in significantly increased reaction times, incomplete reaction, and increased side product formation.

12. The reaction conditions given were developed using (E)-1-acetoxy-1,3-butadiene prepared according to the procedure of McDonald, et al.² with the following modifications (unchecked). Crotonaldehyde (105 g, 125 mL) is added by addition funnel over 1 hr to a refluxing solution of isopropenyl acetate (2.5 mol, 250 g, 275 mL), p-toluenesulfonic acid (anhydrous, 2.0 g) and copper(II) acetate (0.5 g). The mixture is heated at reflux for ~30 min and then the reaction apparatus is set up for distillation. Distillation (bath temp. 110-130°C) is continued for ~2.5 hr until acetone and nearly all unreacted isopropenyl acetate is collected. The distillation residue is cooled to ~25°C and crude product is isolated via vacuum distillation (bp ~32°C, ~7 mm). This crude product typically contains traces of isopropenyl acetate and significant amounts of acetic acid. The crude distillate is dissolved in diethyl ether (500 mL), and carefully mixed with saturated aqueous sodium bicarbonate solution, adding additional anhydrous sodium bicarbonate slowly to the stirring mixture until gas evolution ceases and the pH increases to ~7.0. The layers are separated and the organic phase is washed with brine (300 mL) and dried with magnesium sulfate. The solution is carefully concentrated, and the product is purified by distillation to yield nearly pure (E)-1-acetoxy-1,3-butadiene (~35-50% yield). Frequently, sequential distillations of the product are necessary to ensure the purity of the product obtained. Pure product exhibits the following characteristics: bp 32°/10 mm; TLC: R_f = 0.61 (silica gel, 6:1 hexanes:ethyl acetate); ^1H NMR (500 MHz, CDCl_3) δ : 2.14 (s, 3 H), 5.08 (dd, 1 H, J = 10.5, 0.5), 5.21 (d, 1 H, J = 17.0), 6.03 (dd, 1 H, J = 12.0, 12.0), 6.26 (ddd, 1 H, J = 21.5, 10.5, 10.5), 7.39 (d, 1 H, J = 12.5); ^{13}C NMR (125 MHz, CDCl_3) δ : 20.7 (CH_3), 116.0 (CH), 117.3 (CH_2), 131.7 (CH), 138.6 (CH), 167.8 (C); IR (CDCl_3) cm^{-1} : 3091, 3074,

3041, 1660, 1097; HRMS m/e calcd for $C_6H_8O_2$: 112.0524, found 112.0523; LRMS [EI] (rel %): 112.0 (57), 70.0 (100).

Alternatively, 1-acetoxy-1,3-butadiene is available as a mixture of E,Z-isomers from Aldrich Chemical Company, Inc. When using the commercial reagent, 3.0 eq. (14.8 g, 15.6 mL) is necessary to ensure complete reaction, as the Z isomer does not react.

13. *Caution:* UV radiation is harmful to eyes and skin; the reaction vessel may be wrapped with aluminum foil or the reaction conducted in a closed photochemical reaction cabinet to prevent exposure to the harmful UV rays.

14. The photochemical lamp and power supply may be purchased from Ace Glass Inc., Vineland, N.J., catalog #'s 7825-32 or 7825-40 (lamp) and 7830-60 (power supply).

15. A solid buildup occurs on the immersion well that may slow the reaction considerably. To help minimize this, the submitters suggest a constant purging of the reaction mixture with argon throughout the entire reaction time.

16. Typical TLC data (silica gel, 6:1 hexanes:ethyl acetate) include R_f = 0.61 (1-acetoxy-1,3-butadiene); 0.51, a red spot [tricarbonyl(cycloheptatriene)chromium]; 0.45 a yellow spot (side product that often overlaps with the starting complex); and 0.31 a yellow spot (main intermediate chromium complex).

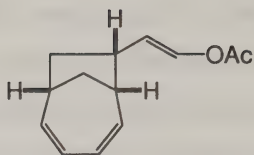
17. Prior to and between washes, the green filter cake cracks and should be "pushed down" with a spatula to form a uniform surface prior to any subsequent washes.

18. TLC at this point (silica gel, 6:1 hexanes: ethyl acetate) shows three spots (UV): R_f = 0.76 (trace orange); 0.55 (side product); 0.47 (main product).

19. Chromatography is performed as follows: a 3.5-cm ID glass column is packed with ~140 g of flash grade silica gel (Merck 230-400 mesh) in petroleum ether and the sample is loaded in minimal petroleum ether. The checkers found that a 5.0-

cm ID glass column packed with ~170 g of Merck 70-270 mesh silica gel gave slightly better separation. Care must be taken during product application to minimize silica gel column separation. The column is eluted, recycling solvent as necessary, until the front running orange band is collected. This band is comprised of trace amounts of unreacted tricarbonyl(cycloheptatriene)chromium. Elution then proceeds using 500 mL of 49:1 petroleum ether: diethyl ether followed by 19:1 petroleum ether: diethyl ether to obtain the product. Prior to elution of the desired $[6\pi+4\pi]$ cycloadduct, the side product, $[6\pi+2\pi]$ cycloadduct (**A**) elutes, usually streaking into the desired product, but it is of little consequence. All fractions containing the desired product are combined and the solvent is removed under reduced pressure. The product sometimes solidifies during solvent removal, but may require seeding with authentic material to promote crystallization.

20. The $[6\pi+4\pi]$ cycloadduct exhibits the following characteristics: bp: 104-107°/1.3 mm; TLC: R_f = 0.47 (silica gel, 6:1 hexanes:ethyl acetate); ^1H NMR (500 MHz, CDCl_3) δ : 2.11 (s, 3 H), 2.12-2.15 (m, 1 H), 2.31 (bd, 1 H, J = 14.0), 2.35-2.47 (m, 2 H), 2.74 (bs, 1 H), 2.92 (bs, 1 H), 5.49 (bd, 1 H, J = 11.0), 5.60-5.65 (m, 1 H), 5.66-5.68 (m, 1 H), 5.73-5.81 (m, 2 H), 5.83-5.88 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ : 21.4 (CH_3), 31.7 (CH_2), 32.9 (CH_2), 37.3 (CH), 42.7 (CH), 76.7 (CH), 124.9 (CH), 127.1 (CH), 128.7 (CH), 133.1 (CH), 135.3 (CH), 137.8 (CH), 170.5 (C); IR (neat) cm^{-1} : 3011, 2924, 2905, 2884, 2872, 1737, 1447, 1430, 1368, 1241, 1199, 1055, 1020; HRMS calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$: m/e 204.11503, found 204.1149; LRMS [EI] (rel %): 204.1 (2), 162.1 (2), 144.1 (20), 129.0 (11), 112.0 (6), 92.0 (100). Purity was determined by 500 MHz ^1H NMR, with the main impurity being the $[6\pi+2\pi]$ cycloadduct **A**.



A

This compound exhibits the following characteristics: TLC: $R_f = 0.35$ (silica gel, 19:1 hexanes:ethyl acetate); ^1H NMR (500 MHz, CDCl_3) δ : 1.58 (ddd, 1 H, $J = 13.5, 9.5, 3.5$), 1.89 (d, 1 H, $J = 12.0$), 2.01 (ddd, 1 H, $J = 13.5, 9.5, 9.5$), 2.10 (s, 3 H), 2.14-2.19 (m, 1 H), 2.61 (dd, 1 H, $J = 12.0, 5.5$), 2.69 (ddd, 1 H, $J = 16.5, 8.5, 4.0$), 2.84 (ddd, 1 H, $J = 19.5, 9.5, 6.0$), 5.58 (d, 1 H, $J = 10.0, 6.0$), 5.62 (dd, 1 H, $J = 12.0, 9.5$), 5.72 (dd, 1 H, $J = 12.0, 7.0$), 5.83 (dd, 1 H, $J = 12.0, 6.5$), 6.10 (dd, 1 H, $J = 10.5, 8.5$), 7.09 (d, 1 H, $J = 12.0$); ^{13}C NMR (125 MHz, CDCl_3) δ : 20.7 (CH_3), 33.3 (CH_2), 36.7 (CH), 42.3 (CH_2), 46.3 (CH), 54.7 (CH), 115.5 (CH), 123.3 (CH), 126.6 (CH), 135.0 (CH), 135.2 (CH), 141.0 (CH), 168.2 (C); IR (neat) cm^{-1} : 3019, 2950, 2931, 2863, 1755, 1370, 1219, 1094; HRMS calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$: m/e 204.11503, found 204.1147; LRMS [EI] (rel %): 204.1 (2), 144.1 (20), 129.1 (7), 112.0 (6), 92.0 (100).

21. The yield reported is that of the submitters and is based on the use of the pure (E)-1-acetoxy-1,3-butadiene. It was found by the checkers that use of a mixture of the E, Z-isomers (as purchased from Aldrich Chemical Company, Inc.) led to an average yield of 73%.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. Wastes containing chromium, aqueous solutions as well as solids, were collected and disposed of separately. Prior to washing, all glassware laden with chromium by-products, were soaked overnight in a solution composed of 15-20 g of copper beads dissolved in ~2 L of 50% aqueous nitric acid. This solution may be kept loosely capped in a fume hood and reused several times prior to disposal.

3. Discussion

Synthetic sequences that employ a cycloaddition step benefit from the convergency and stereoselectivity that characterizes these pericyclic transformations. In recent years, several new methodologies for performing so-called higher-order cycloadditions [e.g., $[6\pi+4\pi]$, $[6\pi+2\pi]$, $[4\pi+4\pi]$, $[4\pi+3\pi]$, etc.] have appeared and are now being used as key transformations in the synthesis of a number of target molecules.³ For example, a number of reports have appeared in which the generation of specific examples of bicyclo[4.4.1]undecatriene ring systems are noted as useful intermediates in the synthesis of cerorubenate sesterterpenes⁴ as well as the ingenane diterpenes.⁵ In particular, the general utility of chromium-mediated $[6\pi+4\pi]$ cycloaddition in the synthesis of several bicyclo[4.4.1]undecatriene systems as potential intermediates in natural product synthesis has been demonstrated,⁶ including the synthesis of members of the taxane and tiglane families.⁷ Furthermore, studies involving cleavage of certain functionalized members of these ring systems, allows for the generation of medium-sized carbocycles.⁸

With these synthetic opportunities in mind, presentation of the methodology used in large scale generation of tricarbonyl(η^6 -cycloheptatriene)chromium(0) as well as an example of $[6\pi+4\pi]$ cycloaddition is timely. Although a specific example of the submitter's higher-order cycloaddition methodology utilizing an electron-rich diene partner is presented, comparable results have also been obtained employing an electron-poor diene, methyl sorbate, with typical yields of 80-85% on a 10-g scale.⁹

Key to this large scale cycloaddition chemistry is the ability to generate large quantities of tricarbonyl(η^6 -cycloheptatriene)chromium(0). The submitters have found that the best results are obtained when the desired complex is generated with the highly reactive and pyrophoric complexation reagent $(\text{CH}_3\text{CN})_3\text{Cr}(\text{CO})_3$.¹⁰ One drawback to this method, however, was the need to scrape solidified $\text{Cr}(\text{CO})_6$ from the reflux condenser during the early stages of the reaction, causing atmospheric exposure to the reactants. For this reason, an engineering control was instituted through development of a reaction vessel (Figure 1) containing a built-in large bore condenser, thereby obviating the need to open the system for scraping and allowing, after subsequent complexation with cycloheptatriene, the isolation of highly pure product complex with little or no additional purification necessary.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

7 α -Acetoxy-(1H β , 6H β)-bicyclo[4.4.1]undeca-2,4,8-triene: Bicyclo[4.4.1]undeca-3,7,9-triene-2-ol, acetate, endo- (\pm)- (12); (129000-83-5)

Tricarbonyl(η^6 -cycloheptatriene)chromium(0): Chromium, tricarbonyl (1,3,5-cycloheptatriene)- (8); Chromium, tricarbonyl[(1,2,3,4,5,6- η)-1,3,5-cycloheptatriene]- (9); (12125-72-3)

Acetonitrile (8,9), (75-05-8)

Chromium hexacarbonyl: HIGHLY TOXIC: Chromium carbonyl (8); Chromium carbonyl (OC-6-11)- (9); (13007-92-6)

Cycloheptatriene: 1,3,5-Cycloheptatriene (8,9); (544-25-2)

Tris(acetonitrile)chromium tricarbonyl: Chromium, tris(acetonitrile)tricarbonyl- (8,9); (16800-46-7)

(E)-1-Acetoxy-1,3-butadiene: 1,3-Butadiene-1-ol acetate, (E)- (9); (35694-20-3)

Crotonaldehyde: Crotonaldehyde, (E)- (8); 2-Butenal, (E)- (9); (123-73-9)

Isopropenyl acetate: 1-Propen-2-ol, acetate (8,9); (108-22-5)

p-Toluenesulfonic acid (8); Benzenesulfonic acid, 4-methyl- (9); (104-15-4)

Cupric acetate monohydrate: Acetic acid, copper(2+) salt, monohydrate (8,9); (6046-93-1)

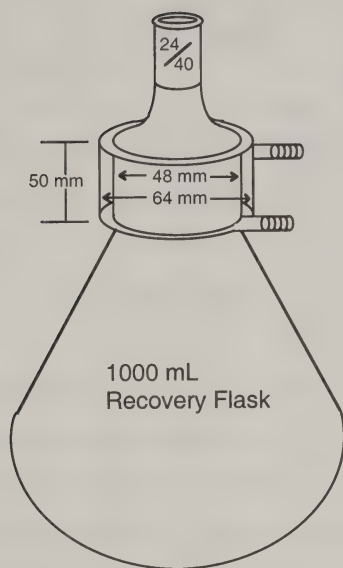


Figure 1

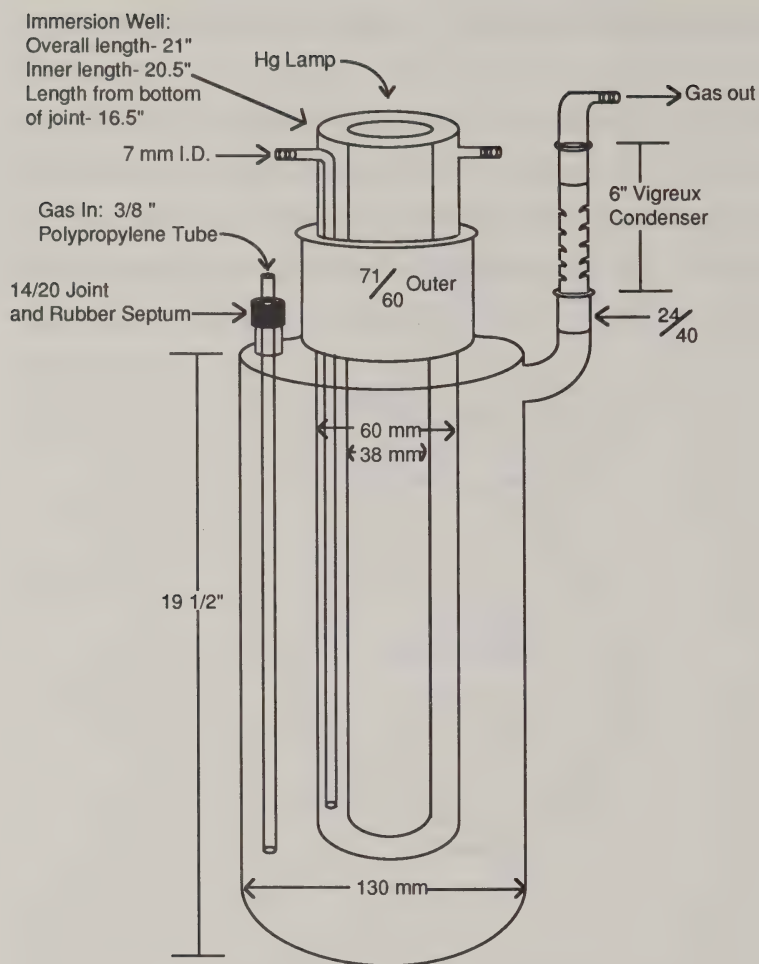
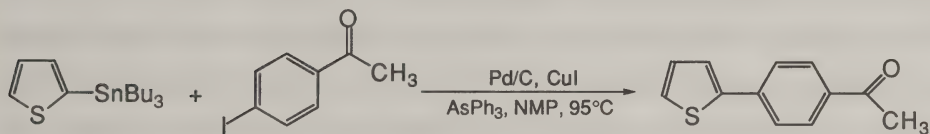


Figure 2: Immersion well photochemical reactor

STILLE COUPLINGS CATALYZED BY PALLADIUM-ON-CARBON WITH
CuI AS A COCATALYST: SYNTHESIS OF
2-(4'-ACETYLPHENYL)THIOPHENE¹



Submitted by Lanny S. Liebeskind² and Eduardo Peña-Cabrera.³

Checked by Jory Wendling and Louis S. Hegedus.

1. Procedure

A 200-mL, flame-dried Schlenk flask is purged with nitrogen and charged with 10.0 g (40.6 mmol) of 4-iodoacetophenone (Note 1), 770 mg (4.1 mmol) of copper(I) iodide (CuI) (Note 2), 2.5 g (8.1 mmol) of triphenylarsine (Note 3), and 150 mL of anhydrous 1-methyl-2-pyrrolidinone (Note 4). The dark solution is degassed for 15 min (nitrogen sparge) and then 14.1 mL (44.7 mmol) of 2-(tributylstannyl)thiophene (Note 5) is added. The reaction flask is immersed in a preheated oil bath at 95°C and 215 mg (0.2 mmol) of 10% palladium on activated carbon (Note 6) is added under a positive nitrogen pressure. The mixture is kept at 95°C for 24 hr (Note 7) and then allowed to cool to 25°C and diluted with 300 mL of ethyl acetate. The dark mixture is poured into 200 mL of an aqueous saturated sodium fluoride solution (Note 8) and stirred vigorously for 30 min. The green-yellow heterogeneous mixture is passed through a sand pad contained in a medium-frit filter, aided by a water aspirator (Note 9). The filtrate is partitioned in a separatory funnel and the aqueous layer is extracted with two 100-mL portions of ethyl acetate. The organic extracts are combined and

stirred with 200 mL of fresh saturated aqueous sodium fluoride solution for 30 min. The mixture is then passed through a sand pad as described above. The pad is rinsed with 50 mL of ethyl acetate. The mixture is partitioned again and the aqueous layer is extracted with two 50-mL portions of ethyl acetate. The organic extracts are combined and washed with five 100-mL portions of water and finally with 100 mL of brine (Note 10). The dark yellow solution is dried over anhydrous magnesium sulfate (MgSO_4) (Note 11) and filtered. The used MgSO_4 is washed with 50 mL of ethyl acetate. The solvent is removed under reduced pressure to give a dark yellow solid that is dissolved in the minimum amount of dichloromethane and adsorbed onto 20 g of silica gel (Note 12). The solvent is thoroughly removed under reduced pressure and the resulting solid is charged into a medium-pressure liquid chromatography column (silica gel, 3 x 15 cm) (Note 13). The product (6.6 g, 80%) (Note 14) is purified as described by Baeckström et al.⁴ (Note 15).

2. Notes

1. 4-Iodoacetophenone was purchased from Aldrich Chemical Company, Inc., and used without purification.

2. Copper(I) iodide was purchased from Aldrich Chemical Company, Inc., and purified according to a literature procedure.⁵

3. *Caution: Triphenylarsine is highly toxic and must be handled with gloves in a well-ventilated hood.* It was purchased from Aldrich Chemical Company, Inc., and used as received.

4. Anhydrous 1-methyl-2-pyrrolidinone was purchased from Aldrich Chemical Company, Inc., and used without further drying. The water content was determined to be 117 ppm using a Coulomatric K-F Titrimer.

5. 2-(Tributylstannyl)thiophene was purchased from Aldrich Chemical Company, Inc., and is used without additional purification.

6. 10% Palladium on activated carbon was purchased from Alpha Division.

7. The reaction can be monitored by quenching small aliquots with water and extracting with a small amount of diethyl ether. The ethereal layer is spotted on an analytical silica gel TLC plate (0.25 mm thickness, from EM Separations Technology) (10% ethyl acetate in hexanes, using 254 nm UV light to visualize the spots). The following are the R_f s of the components of the mixture: 2-(tributylstannyl)thiophene (0.86), triphenylarsine (0.62), 4-iodoacetophenone (0.48), and 2-(4'-acetylphenyl)-thiophene, (0.38 fluorescent). Trace amounts of 4-butylbenzophenone (R_f , 0.52) were observed at the end of the reaction.

8. *Caution: Sodium fluoride is highly toxic and should be handled with gloves in a well-ventilated hood.* It was purchased from Spectrum Chemical Mfg. Corp. and used without purification.

9. If crystallization underneath the frit occurs during the filtration process, the sand pad is washed with 20 mL of ethyl acetate. The sand pad was changed three times during the filtration of the whole mixture to avoid clogging.

10. The washings are necessary to remove all the 1-methyl-2-pyrrolidinone.

11. Anhydrous magnesium sulfate was obtained from EM Science.

12. Silica gel 60, particle size 0.040-0.063 mm (230-400 mesh) was obtained from EM Separation Technology.

13. The medium-pressure liquid chromatography system (MPLC) was purchased from Baeckström SEPARO AB.

14. The product (a golden flaky solid) exhibits the following properties: mp 118-119°C; IR (CH_2Cl_2) cm^{-1} : 1680, 1601, 1270; ^1H NMR (300 MHz, CDCl_3) δ : 2.6 (s, 3 H), 7.1 (m, 1 H), 7.3 (d, 1 H, $J = 5$), 7.4 (d, 1 H, $J = 3.8$), 7.7 (d, 2 H, $J = 8$), 8.0 (d, 2 H, $J = 9$); ^{13}C NMR (75.5 MHz, CDCl_3) δ : 26.5, 124.6, 125.6, 126.4, 128.3, 129.1, 135.7,

138.7, 142.9, 197.2. Anal. Calcd for $C_{12}H_{10}OS$: C, 71.30; H, 5.00; S, 15.90. Found: C, 71.14; H, 5.03; S, 15.77. (The material obtained by the checkers was a very pale yellow flaky solid.)

15. The purification was carried out using a hexanes/dichloromethane gradient (200 mL of each gradient solution). The gradient started with hexanes at a flow rate of 25 mL/min and the concentration of dichloromethane was increased each time by 10%. A total of fifty 30-mL fractions were collected. Under these conditions, most of the triphenylarsine used was recovered and recycled. (The checkers purified the material using conventional flash chromatography techniques. The crude product adsorbed on 20 g of flash silica gel was dry packed on a 6-cm x 14-cm column of flash silica gel. Elution with 750 mL of hexanes followed by 500 mL each of a hexane/dichloromethane gradient starting with 10% dichloromethane (CH_2Cl_2)/hexanes and finishing with 100% CH_2Cl_2 . A total of fifty 100-mL fractions were collected. The separation was monitored by analytical TLC as described in Note 7.)

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

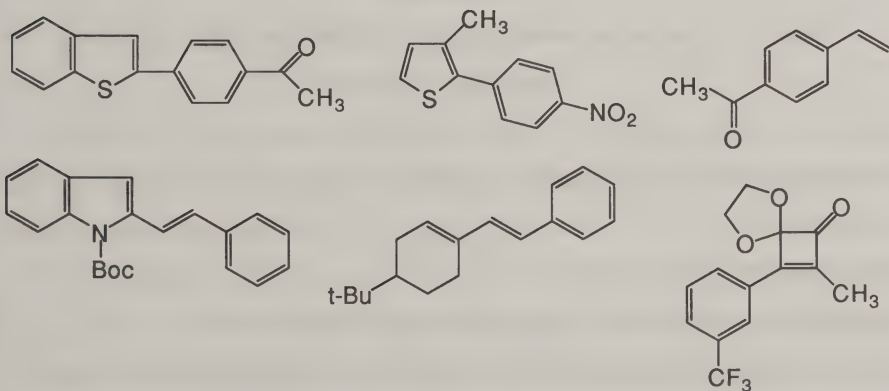
The rate-enhancing influence of Cu(I) salts (the so-called "Copper Effect") in normally nonproductive and sluggish Stille couplings was first pointed out by Liebeskind et al.⁶ in 1990. A greater insight into this phenomenon was obtained later by Farina and co-workers.⁷ A number of modifications of the Stille reaction have since

been reported. Among them are the cross-coupling of organostannanes with organic halides promoted by stoichiometric amounts of Cu(I) salts,⁸ and the Cu(I)- or Mn(II)-catalyzed cross-coupling of organostannanes with iodides in the presence of sodium chloride.⁹

It was also discovered that aryl and vinyl iodides, bromides, and triflates participated efficiently in cross-coupling reactions with organostannanes when catalyzed by palladium-on-carbon in the presence of Cu(I) as cocatalyst.¹

The best conditions were found to be: Pd/C (0.5 mole%), Cu(I) (10 mole%), and AsPh₃ (20 mole%). Besides the advantage of using a stable form of Pd(0), the yield of the products under these conditions was better than that obtained using tris(dibenzylideneacetone)palladium [Pd₂(dba)₃] as the source of Pd(0). Similarly, a slightly lesser amount of the homocoupled product was observed using the Pd/C protocol. Although a significant amount of AsPh₃ is necessary for cross-coupling to take place, it can be efficiently recovered (and recycled) at the end of the reaction by column chromatography.

Other products prepared using the Pd/C protocol are:



1. The original report was published elsewhere: Roth, G. P.; Farina, V.; Liebeskind, L. S.; Peña-Cabrera, E. *Tetrahedron Lett.* **1995**, 36, 2191.
2. Chemistry Department, Emory University, 1515 Pierce Dr., Atlanta, GA 30322.
3. Facultad de Química, Universidad de Guanajuato, Col. Noria Alta S/N, Guanajuato, Gto. 36000, Mexico.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4-Iodoacetophenone: Acetophenone, 4'-iodo- (8); Ethanone, 1-(4-iodophenyl)- (9); (13329-40-3)

Copper(I) iodide (8,9); (7681-65-4)

Triphenylarsine: HIGHLY TOXIC: Arsine, triphenyl- (8,9); (603-32-7)

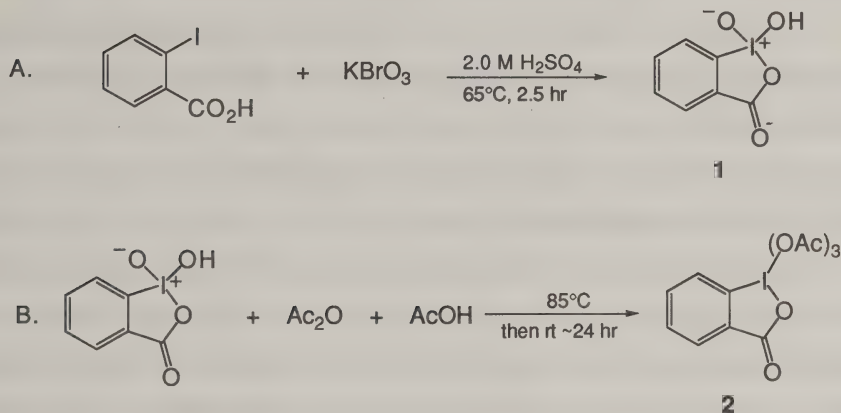
1-Methylpyrrolidinone: 2-Pyrrolidinone, 1-methyl- (8,9); (872-50-4)

2-(Tributylstannyl)thiophene: Stannane, tributyl-2-thienyl- (9); (54663-78-4)

Sodium fluoroide (8,9); (7681-49-4)

THE DESS-MARTIN PERIODINANE:

1,1,1-TRIACETOXY-1,1-DIHYDRO-1,2-BENZIODOXOL-3(1H)-ONE (1,2-Benziodoxol-3(1H)-one, 1,1,1-tris(acetyloxy)-1,1-dihydro-)



Submitted by Robert K. Boeckman, Jr., Pengcheng Shao, and Joseph J. Mullins.¹

Checked by Kevin P. Minbiole and Amos B. Smith, III.

1. Procedure

Caution: Compounds **1** and **2** are heat- and shock-sensitive compounds, showing exotherms when heated ($>130^\circ\text{C}$). All operations should be conducted behind an explosion shield.

A. *1-Hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide (1)*. A 2-L, three-necked, round-bottomed flask, fitted with a mechanical stirrer, condenser, and an immersion thermometer is charged with 80.0 g (0.48 mol) of potassium bromate (KBrO_3) and 750 mL of 2.0 M sulfuric acid (Notes 1-3). The resulting clear solution is heated to 60°C in an oil bath and 80.0 g of finely powdered 2-iodobenzoic acid (0.323 mol) is added in

~10-g portions over 40 min (Notes 4, 5). The solution becomes red-orange, bromine vapor is evolved, and a white solid begins to separate (Note 6). After the addition is complete, the temperature is maintained at an internal temperature of 65°C for 2.5 hr (Note 3).

The reaction mixture is cooled to 2-3°C in an ice-water bath, and the resulting solids are collected by vacuum filtration (Notes 7, 8). The filter cake is thoroughly washed successively with 500 mL of cold deionized water, 2 x 80 mL of absolute ethanol, and 500 mL of cold deionized water affording 88.2 g (98% of theoretical) of moist solid iodine oxide **1** (Notes 9, 10).

B. 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (2). A 1-L, three-necked, round-bottomed flask, equipped for magnetic stirring and fitted with an immersion thermometer, is charged with 88.2 g of the moist solid iodine oxide **1**, 150 mL of glacial acetic acid, and 300 mL of acetic anhydride (Note 11). The flask is flushed with dry argon, and maintained under a dry argon atmosphere. Magnetic stirring is commenced, and the mixture is heated to 85°C (internal temperature) over 30 min by means of an oil bath, and kept at this temperature until all the solids dissolve (~20 min) to afford a colorless to clear yellow solution (Note 12). Heating and stirring are discontinued and the reaction mixture is allowed to cool slowly to room temperature in the oil bath for 24 hr. A large quantity of colorless crystals separate during this time (Note 13). The resulting crystalline solids are isolated by careful vacuum filtration in the reaction vessel under argon using a fritted adapter followed by washing the solids with three 80-mL portions of anhydrous ether and subsequent vacuum filtration in the reaction vessel as above (Notes 14, 15). Residual solvent is removed under vacuum affording 101.0 g (74% yield over 2 steps) of periodinane **2** as a white, free-flowing crystalline solid that is largely or completely soluble (slightly cloudy to clear solution) in chloroform and methylene chloride and is sufficiently pure (~95%) to be suitable for use in oxidations (Notes 16-19).

2. Notes

1. Although no problems with explosion of **1** or **2** have been encountered in the use of this procedure, prudence dictates that all operations should be conducted behind an explosion shield.²⁻⁴

2. Potassium bromate (>99.5%) was used as received from Fluka Chemical Co.

3. Use of higher concentration sulfuric acid (~2.0 M) than traditionally employed is crucial to allow complete conversion of the 2-iodobenzoic acid to **1**.² In the submitters hands, use of lower concentrations (~0.5 M) of sulfuric acid at 60°C led to exclusive formation of 1-hydroxy-1,2-benziodoxol-3(1H)-one. When lower concentrations of sulfuric acid are employed, higher temperatures are required to effect oxidation, as judged by the initiation of bromine evolution. One of the factors leading to the lack of reproducibility in the preparation of **2** results from incomplete conversion to **1**.

4. 2-Iodobenzoic acid (Aldrich Chemical Company, Inc.) was recrystallized from toluene (100 g/500 mL).

5. The bromine vapors are vented by inverting a funnel over the open condenser (allowing a small gap between the funnel and the condenser top) with the stem attached to a gas washing bottle containing saturated aqueous sodium thiosulfate solution, which is in turn, connected to a water aspirator.

6. Addition of the 2-iodobenzoic acid to the bromate-aqueous acid mixture results in an easily controlled, smooth reaction and an easily stirred reaction mixture. The stirring rate should be regulated such that splashing is minimized and solids do not accumulate on the walls or roof of the reaction vessel. Any solids which adhere to the sides or roof of the reaction vessel above the level of the liquid should be washed back into the reaction mixture with the minimum amount of 2M sulfuric acid. Addition

of the bromate to the mixture of iodobenzoic acid and sulfuric acid as originally described,² led to a thick precipitate that was difficult to stir, and the accumulation of solid on the walls of the reaction vessel. Given the thermal sensitivity of **1**, the present procedure appears much safer (Note 1).^{4,5}

7. The reaction mixture is thoroughly cooled prior to filtration and cold water is employed for washing because of the low but appreciable solubility of **1** in water (~0.3 g/100 mL).

8. Use of a ceramic Büchner funnel with coarse filter paper is recommended to avoid scraping a glass frit during removal of **1**. A rubber spatula is recommended for stirring and manipulation of the filter cake. The filter cake can be conveniently removed from the funnel by applying a small amount of air pressure to the stem.

9. All washes were conducted by slurring the solids on the filter bed with a rubber spatula followed by application of the vacuum. In view of the sensitivity (Note 10) of this intermediate and/or the periodinane **2**,³ care should be taken to avoid thorough drying of the solid oxide **1**. The use of the ethanol washes appears essential to reduce further the explosion hazard. These washes presumably destroy any unreacted bromate present in the solids. The submitters have observed that another of the factors leading to the lack of reproducibility in the preparation of the periodinane is associated with the incomplete removal of ethanol after the washing in an effort to avoid drying the oxide **1**. The presence of ethanol in the oxide results in destruction of the periodinane **2** as it is formed in the next transformation. The use of a final aqueous wash serves to remove the ethanol and keep the oxide moist. This moisture is not detrimental in the next reaction. Small samples of moist solid **1** were also washed successively with reagent grade acetone and anhydrous ether, and residual solvent was removed under vacuum. Identical overall yields of **2** were obtained by both procedures.

10. Recently, the ^1H NMR of **1** in d_6 DMSO has been reported.⁵ The ^1H NMR spectrum of **1** prepared as described above was identical to that reported: ^1H NMR (400 MHz in d_6 DMSO) δ as follows: 7.84 (t, 1 H, $J = 14.8$), 7.99 (t, 1 H, $J = 7.9$), 8.02 (d, 1 H, $J = 14.8$), 8.15 (d, 1 H, $J = 7.9$). Incomplete conversion results in impurity peaks at δ 7.71 (t or m, 1 H) from 1-hydroxy-1,2-benziodoxol-3(1H)-one or from both 1-hydroxy-1,2-benziodoxol-3(1H)-one and 2-iodobenzoic acid (if both are present), and δ 7.48 (t, 1 H) and 7.25 (t, 1 H) from 2-iodobenzoic acid (if present). Conversion to **1** can also be conveniently assayed by reduction of a weighed sample of **1** with excess aqueous sodium iodide and titration of the resulting iodine with standardized 1N sodium thiosulfate solution to a colorless endpoint (1 mmol of thiosulfate per mmol of **1** required). The physical properties of authentic **1** are also diagnostic. From the present procedure, **1** is obtained as a somewhat granular, easily-filtered solid. 1-Hydroxy-1,2-benziodoxol-3(1H)-one or impure samples of **1** containing significant amounts of 1-hydroxy-1,2-benziodoxol-3(1H)-one and possibly 2-iodobenzoic acid are obtained as sticky precipitates which are difficult to filter and wash, and which retain substantial amounts of solvent. **Samples of the moist oxide **1** were found to exhibit impact sensitivity and were found to exhibit exotherms upon heating ($> 130^\circ\text{C}$) characteristic of an explosive material upon examination by differential scanning calorimetry.**²⁻⁴

11. Glacial acetic acid and acetic anhydride were used as received from J. T. Baker Chemical Co. The checkers used glacial acetic acid as received from Fisher Scientific and acetic anhydride (99%) as received from Aldrich Chemical Company, Inc.

12. Monitoring the reaction by NMR immediately upon dissolution of **1** indicated that the major product was the desired **2** accompanied by a minor amount of what is likely the I(V) monoacetate and a small amount ($<5\%$) of 1-acetoxy-1,2-benziodoxol-3(1H)-one possibly resulting from incomplete oxidation to **1** (see Note 17 for chemical

shift values). Heating the reaction mixture for 3 hr at 110°C results in complete conversion to 1-acetoxy-1,2-benziodoxol-3(1H)-one; thus prolonged heating should be avoided.

13. Slow cooling affords better product crystallinity and easier handling during isolation of **2**.

14. Ether was dried and deoxygenated by distillation from sodium benzophenone ketyl under nitrogen just prior to use. Experience has shown that the quality of reagent **2** is most directly affected by 1) failure to control conversion to the triacetate and 2) exposure to moisture during filtration and other manipulations performed during isolation of the periodinane. Extensive hydrolysis of **2** was observed when washing with ether was conducted in a humid environment.

15. Vacuum filtration was accomplished with a water aspirator fitted with a drying tube. A gas inlet tube with a Teflon stopcock and a medium to coarse porosity glass fritted disc sealed in the bottom of the joint was employed for filtration in the flask. The outlet of the fritted adapter is connected to a filter flask that is attached to a water aspirator, and argon is introduced to equalize pressure in the flask during filtration. The fritted outlet adapter can be purchased from Ace Glass Co., Vineland, NJ (Cat. No. 5295-16-SP). The checkers used a similar adapter from United Glass Technologies. A glove bag or Schlenk filtration is also suitable to effect filtration under an inert atmosphere when the humidity is high.



16. The submitters reported a two-step yield of 111.0 g (80%).

17. The purity of the Dess-Martin periodinane (**2**) was assayed by treatment of **2** (1 equiv) with an excess of benzyl alcohol (2 equiv) in methylene chloride (CH_2Cl_2) followed by analysis of the reaction mixture for benzaldehyde by capillary vapor phase chromatography (15-m fused silica capillary column, Durawax DX3 stationary phase, 120°C). After correction for response factors, the purity was established to be $\geq 95\%$.

18. The Dess-Martin periodinane (**2**) had ^1H NMR (300 MHz in CDCl_3) δ as follows: 1.99 (s, 6 H), 2.32 (s, 3 H), 7.91 (t, 1 H, $J = 7.4$), 8.09 (t, 1 H, $J = 8.1$), 8.29 (d, 2 H, $J = 8.1$). Minor impurity peaks were observed at δ 8.39 (d), 8.21 (d), 8.00 (d), 7.27 (s), and 2.08 (s) (possibly the mono acetate); ^{13}C NMR (75 MHz in CDCl_3) δ : 20.2, 20.4, 125.9, 126.5, 131.7, 133.8, 135.8, 142.2, 166.1, 174.0, 175.7. The checkers note that a freshly opened bottle of deuteriochloroform (CDCl_3) was required to dissolve **2** and that drying of older CDCl_3 by running the solvent through potassium carbonate (K_2CO_3) did not facilitate dissolution. The submitters observed the same phenomenon and believe that traces of acid in the fresh CDCl_3 may be responsible for this observation.

19. The Dess-Martin periodinane (**2**) can be stored in a dark bottle under argon at $\sim -20^\circ\text{C}$ in a freezer.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The Dess-Martin periodinane [1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (**2**)] is one of several 12-I-5 periodinane species developed by J. C. Martin

and co-workers, and has found wide acceptance and utility for the selective oxidation of primary and secondary alcohols to carbonyl compounds.^{2,6} The present procedure is a variation of the Martin procedure and is based heavily upon it.² Modified preparations have been reported by Ireland and Schreiber.⁷ The reported explosiveness of samples of impure **2**³ has prompted a more thorough examination of the properties of **2**.² Possible impurities that could be responsible for rendering the samples explosive are **1** and/or the monoacetate derivatives of **1** and **2** that could arise by incomplete oxidation to **1** or hydrolysis of **2** on storage. Samples of **2** that indicate the presence of significant quantities of **1** or the monoacetate derivatives of **1** and **2** as judged by ¹H NMR should be handled with caution. *Although these investigations were inconclusive as to the precise nature of the impurity/ies that rendered the impure samples of 2 explosive, fresh samples of crude moist 1 were found to be both impact and heat sensitive, decomposing explosively under confinement. Pure 2 is significantly less temperature and impact sensitive; nevertheless, it should be handled with appropriate caution as a potentially explosive material.*⁴

The Dess-Martin periodinane (**2**) has found wide utility as a selective oxidant in sensitive, highly functionalized intermediates commonly encountered in the synthesis of natural products and related complex molecules.² The Dess-Martin periodinane (**2**) has several advantages over other commonly employed oxidizing agents such as chromium(VI)-based reagents and dimethyl sulfoxide (DMSO)-based oxidations including nearly ideal stoichiometry, mild non-acidic or mildly acidic reaction conditions, shorter reaction times, relative ease in the preparation and storage of the reagent, simplified workups with easy removal of the by-products of oxidation, the ease of safe disposal of residues, and the lower toxicity of the the reagents and by-products [relative to chromium(VI) reagents in particular].²

A selection of cases in which **2** has been found to be particularly efficacious is given in the Table. Additional examples are cited in references 1 and 5. Particularly noteworthy examples include the oxidation of acid- and base-sensitive systems, systems containing sulfur and selenium, and 1,3-diols to 1,3-dicarbonyl compounds. Use of chromium reagents in these latter cases often leads to fragmentation products.

TABLE

	\longrightarrow		80% ⁸
	\longrightarrow		100% ⁹
	\longrightarrow		75% ¹⁰
	\longrightarrow		58% ¹¹
	\longrightarrow		$\sim 100\%$ ¹²
	\longrightarrow		86% ¹³
	\longrightarrow		70% ¹⁴
	\longrightarrow		73% ¹⁵

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4. Differential scanning calorimetry and impact studies on **1** and **2** were performed by the courtesy of Dr. David Coffen and his colleagues of Hoffmann La-Roche Inc., and Dr. Ichiro Shinkai and his colleagues of Merck Co. Both moist and partially dried samples of **1** were found to exhibit impact sensitivity and large exotherms characteristic of potentially explosive deflagration were observed beginning at temperatures above 140°C. Samples of pure **2** appeared somewhat less impact sensitive, and had smaller exotherms beginning at ~170°C, but prudence dictates that **2** be handled with appropriate precautions as well.
5. Recently, an alternative preparation of **1** employing oxone as the oxidant has been reported: Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one: 1,2-Benziodoxol-3(1H)-one, 1,1,1-tris(acetyloxy)-1,1-dihydro- (11); (87413-09-0)

1-Hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide: 1,2-Benziodoxol-3(1H)-one, 1-hydroxy-, 1-oxide (10); (61717-82-6)

Potassium bromate: Bromic acid, potassium salt (8,9); (7758-01-2)

2-Iodobenzoic acid: Benzoic acid, o-iodo- (8); Benzoic acid, 2-iodo- (9); (88-67-5)

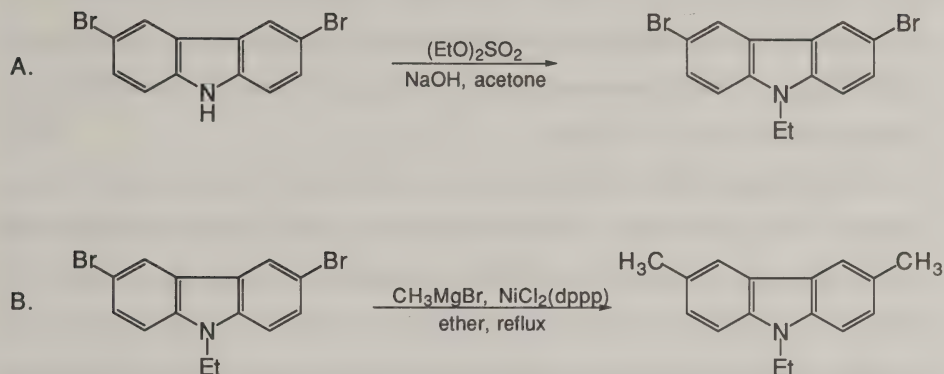
Bromine (8,9); (7726-95-6)

Glacial acetic acid: Acetic acid (8,9); (64-19-7)

Acetic anhydride (8); Acetic acid anhydride (9); (108-24-7)

9-ETHYL-3,6-DIMETHYLCARBAZOLE (DMECZ)

(9H-Carbazole, 9-ethyl-3,6-dimethyl-)



Submitted by Jason R. Buck, Minnie Park, Zhiwei Wang, Daniel R. Prudhomme, and Carmelo J. Rizzo.¹

Checked by Gilles Chambournier and David J. Hart.

1. Procedure

A. *3,6-Dibromo-9-ethylcarbazole*. In an oven dried, 1-L, round-bottomed flask equipped with a magnetic stir bar and a rubber septum are placed 3,6-dibromocarbazole (10.0 g, 31.0 mmol) (Note 1) and sodium hydroxide pellets (1.2 g, 30.0 mmol) in 500 mL of dry acetone (Note 2) under an argon atmosphere. Diethyl sulfate (4.1 mL, 31.0 mmol) (Note 3) is added dropwise over 15 min to the stirred reaction mixture at room temperature. After the addition, the reaction is stirred for 8 hr at which time all solids are removed by filtration and the solvent is removed under reduced pressure to give a yellow solid. The residue is dissolved in ethyl acetate (200 mL) and successively washed with aqueous saturated sodium bicarbonate (3 x 75

mL), brine (3 x 75 mL) and water (3 x 75 mL). The organic layer is dried over sodium sulfate, filtered and the solvent removed under reduced pressure to give a pale yellow solid. Recrystallization from 95% ethanol (ca. 350 mL) gives 3,6-dibromo-9-ethylcarbazole (8.85 g, 81% yield) as white needles, mp 139-141°C (lit.^{2a} mp 137-138°C) (Note 4). The filtrate is evaporated and the resulting solid recrystallized to give additional product (0.24 g, 2% yield).

B. 9-Ethyl-3,6-dimethylcarbazole. In an oven-dried, 1-L, three-necked, round-bottomed flask equipped with a magnetic stir bar, a reflux condenser and a rubber septum are placed 3,6-dibromo-9-ethylcarbazole (7.1 g, 20.0 mmol) and [1,3-bis(diphenylphosphino)propane]nickel(II) chloride (0.54 g, 1.0 mmol) (Note 5) in 500 mL of dry ether (Note 6) under an argon atmosphere (Note 7). To the stirred solution at room temperature is added methylmagnesium bromide (30 mL, 60.0 mmol) (Note 8) dropwise over 20 min via an addition funnel. During the addition, the color of the solution turns from orange to yellow to brown. After the addition, the reaction mixture is heated at reflux for 2 hr at which time the reaction is judged complete by TLC analysis. The reaction mixture is cooled to room temperature, then carefully quenched with aqueous saturated ammonium chloride (25 mL) at which point a brown precipitate forms. All the contents of the reaction are transferred to a separatory funnel and successively washed with aqueous saturated sodium bicarbonate (3 x 50 mL), brine (3 x 50 mL) and deionized water (3 x 50 mL). The combined aqueous layers are extracted with ethyl acetate (3 x 50 mL). The combined organic extracts are dried over sodium sulfate, filtered and the solvent is removed under reduced pressure to give a yellow solid. Recrystallization from ethanol gives 9-ethyl-3,6-dimethylcarbazole (3.62 g, 81% yield) as white needles, mp 57-58°C (lit.^{2a} mp 62-63°C) (Note 9). The filtrate is evaporated and the resulting solid recrystallized from ethanol to give additional product (0.39 g, 9% yield).

2. Notes

1. 3,6-Dibromocarbazole (99%) was obtained from Aldrich Chemical Company, Inc., and was recrystallized from ethanol before use.

2. ACS grade acetone was dried over activated four angstrom molecular sieves.

3. Diethyl sulfate (HIGHLY TOXIC; CANCER SUSPECT AGENT) was obtained from Aldrich Chemical Company, Inc., and used as received.

4. The spectra are as follows: ^1H NMR (CDCl_3) δ : 1.39 (t, 3 H, $J = 7.2$), 4.29 (q, 2 H, $J = 7.2$), 7.26 (d, 2 H, $J = 8.7$), 7.55 (dd, 2 H, $J = 8.7, 1.9$), 8.12 (d, 2 H, $J = 1.9$); ^{13}C NMR (CDCl_3) δ : 13.7 (CH_3), 37.8 (CH_2), 110.1 (CH), 111.9 (C), 123.3 (CH), 123.5 (C), 129.0 (CH), 138.8 (C); MS (EI): m/e (relative intensity) 355 (48), 353 (100), 351 (52), 340 (48), 338 (92), 336 (46). Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{Br}_2\text{N}$: C, 47.84; H, 3.16. Found: C, 47.63; H, 3.13.

5. [1,3-Bis(diphenylphosphino)propane]nickel(II) chloride (99%) was purchased from Strem Chemical and used as received.

6. Diethyl ether was freshly distilled from a sodium/benzophenone ketyl.

7. Gentle warming with a heat gun may be required to dissolve completely 3,6-dibromo-9-ethylcarbazole in ether.

8. Methylmagnesium bromide was purchased from Aldrich Chemical Company, Inc. as a 3.0 M solution in diethyl ether and used as received.

9. The spectra are as follows: ^1H NMR (CDCl_3) δ : 1.14 (t, 3 H, $J = 7.2$), 2.58 (s, 6 H), 4.34 (q, 2 H, $J = 7.2$), 7.31 (s, 4 H), 7.91 (s, 2 H); ^{13}C NMR (CDCl_3) δ : 13.7 (CH_3), 21.3 (CH_3), 37.5 (CH_2), 108.0 (CH), 120.3 (CH), 122.8 (C), 126.7 (CH), 127.6 (C), 138.4 (C); MS (EI): m/e (relative intensity) 223 (69), 208 (100). Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{N}$: C, 86.05; H, 7.68. Found: C, 85.35; H, 7.70.

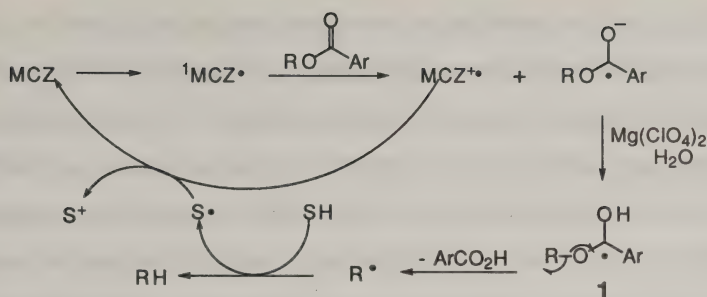
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Since its introduction by Barton and McCombie, the deoxygenation of thionocarbonyl derivatives of alcohols has become an important synthetic reaction and a valuable method for the generation of carbon-centered radicals.^{3,4} Xanthates, thionobenzotes, thionocarbonyl imidazolides, aryloxy thionocarbonate, N-phenylthionocarbamates and oxalate esters are conveniently deoxygenated with tin or silicon hydrides in boiling benzene or toluene.^{4,5}

Saito demonstrated that benzoates and m-(trifluoromethyl)benzoates of secondary alcohols could be deoxygenated via a photoinduced electron-transfer (PET) mechanism using 9-methylcarbazole (MCZ) as the electron donor.^{6,7} The mechanism involves an excited state electron-transfer from MCZ to the benzoate to give the MCZ/benzoate radical ion pair; solvent cage escape is promoted by salts such as magnesium perchlorate. Protonation of the benzoate radical anion gives radical **1**, which undergoes β -scission to the deoxygenation radical. Hydrogen atom transfer from the solvent (i.e., 2-propanol) gives the deoxygenated product. Oxidation of the solvent radical by MCZ radical cation regenerates the donor. In principle, the donor could be used in substoichiometric amounts since it is regenerated; however, in practice one full equivalent of MCZ is necessary for the PET deoxygenation.



The submitters reasoned that the radical cation of MCZ was undergoing side reactions or degradation faster than the steps leading to the regeneration of MCZ. The radical cations of carbazoles have been previously studied by cyclic voltammetry (CV) and it was found that MCZ was irreversibly oxidized, indicating that the radical cation undergoes side reactions faster than the CV time scale.² The electrochemical oxidation of some 9-alkyl carbazoles substituted at the 3- and 6-positions showed improved reversibility, indicating that the radical cations were longer-lived. The submitters demonstrated that 10-20 mol % of 9-ethyl-3,6-dimethylcarbazole (DMECZ) could efficiently deoxygenate benzoate and *m*-(trifluoromethyl)benzoates in high yields (Table).⁸ The increased lifetime of the radical cation of DMECZ allows for the donor to be regenerated and thus it can be used in substoichiometric amounts. Importantly, it appears that DMECZ is a more reactive donor. Because of the toxicity of tin species, there has been interest in developing alternative methods for the Barton and related deoxygenation reactions and some success has been achieved.⁹ The photodeoxygenation not only avoids toxic tin species, but also it is conducted in relatively benign solvents (2-propanol/water). In addition, the deoxygenation is carried out at room temperature or below, and benzoyl derivatives are attractive because of their easy synthetic access under mild and neutral conditions.

9-Ethyl-3,6-dimethylcarbazole was previously synthesized in four steps beginning with the formylation of 9-ethylcarbazole to give 9-ethylcarbazole-3-carboxaldehyde which is now commercially available.¹⁰ Wolff-Kishner reduction, formylation of the 6-position, and a second Wolff-Kishner reduction gives DMECZ. The reported overall yield for the final three steps is 45%. The present procedure provides quantities of the desired compound in high overall yield by a shorter, more convenient sequence. The desired material was also prepared by a nickel-catalyzed cross-coupling of 3,6-dibromo-9-ethylcarbazole with methylmagnesium bromide (Corriu-Kumada coupling).¹¹ 3,6-Dibromo-9-ethylcarbazole was prepared by N-alkylation of commercially available 3,6-dibromocarbazole with diethyl sulfate. Alternatively, 3,6-dibromo-9-ethylcarbazole could be prepared by the bromination of 9-ethylcarbazole (Br₂, acetic acid, 0°C); however, this method also produced significant quantities of 1,3,6-tribromo-9-ethylcarbazole.

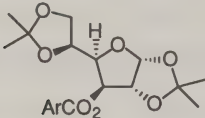
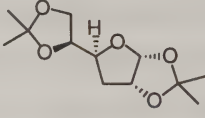
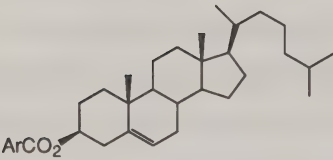
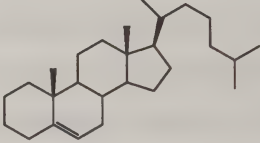
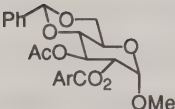
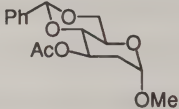
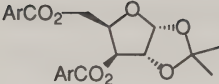
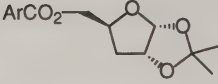
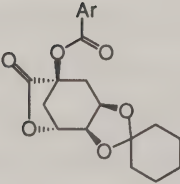
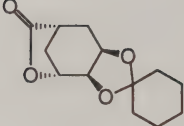
Acknowledgments: This work was supported by Grant #DHP-172 from the American Cancer Society.

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TABLE

PHOTOINDUCED ELECTRON-TRANSFER DEOXYGENATION OF BENZOATES AND
 m-(TRIFLUOROMETHYL)BENZOATES WITH 9-ETHYL-3,6-DIMETHYLCARBAZOLE

Substrate	Product and Yield
 <p>Ar = m-CF₃C₆H₄ - Ar = C₆H₅ -</p>	 <p>84% 86%</p>
 <p>Ar = m-CF₃C₆H₄ - Ar = C₆H₅ -</p>	 <p>92% 90%</p>
 <p>Ar = m-CF₃C₆H₄ - Ar = C₆H₅ -</p>	 <p>85% 84%</p>
 <p>Ar = m-CF₃C₆H₄ - Ar = C₆H₅ -</p>	 <p>64% 70%</p>
 <p>Ar = m-CF₃C₆H₄ - 160</p>	 <p>60%</p>

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

9-Ethyl-3,6-dimethyl-carbazole: 9H-Carbazole, 9-ethyl-3,6-dimethyl- (9); (51545-42-7)

3,6-Dibromo-9-ethylcarbazole: Carbazole, 3,6-dibromo-9-ethyl- (8); 9H-Carbazole, 3,6-dibromo-9-ethyl- (9); (33255-13-9)

3,6-Dibromocarbazole: Carbazole, 3,6-dibromo- (8); 9H-Carbazole, 3,6-dibromo- (9); (6825-20-3)

Diethyl sulfate: HIGHLY TOXIC; CANCER SUSPECT AGENT: Sulfuric acid, diethyl ester (8,9); (64-67-5)

[1,3-Bis(diphenylphosphino)propane]nickel(II) chloride: CANCER SUSPECT AGENT:

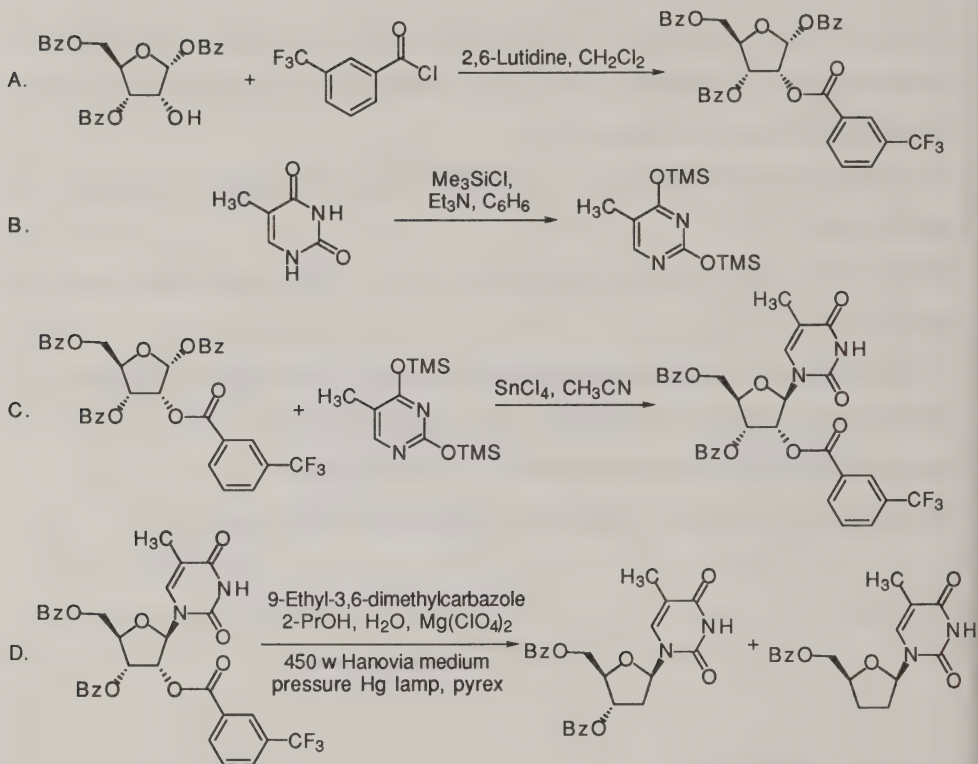
Nickel, dichloro[trimethylenebis[diphenylphosphine]]- (8); Nickel, dichloro[1,3-propanediylbis[diphenylphosphine]-P,P']- (9); (15629-92-2)

Methylmagnesium bromide: Magnesium, bromomethyl- (8,9); (75-16-1)

SYNTHESIS OF 2'-DEOXYRIBONUCLEOSIDES:

β -3',5'-DI-O-BENZOYLTHYMIDINE

(Thymidine, 3',5'-dibenzoate)



Submitted by Daniel R. Prudhomme, Minnie Park, Zhiwei Wang, Jason R. Buck, and Carmelo J. Rizzo.¹

Checked by Gilles Chambournier, Jane Djung, and David J. Hart.

1. Procedures

A. *1,3,5-O-Tribenzoyl-2-O-[(3-trifluoromethyl)benzoyl]- α -D-ribofuranose*. In an oven-dried, 500-mL, two-necked, round-bottomed flask equipped with a magnetic stir bar and a rubber septum is placed 1,3,5-tri-O-benzoyl- α -D-ribofuranose (5.0 g, 10.8 mmol) (Note 1) and 2,6-lutidine (1.4 g, 13.0 mmol) (Note 2) in 200 mL of dry dichloromethane (Note 3) under an argon atmosphere. The reaction mixture is cooled to 0°C and 3-(trifluoromethyl)benzoyl chloride (3.3 g, 16.2 mmol) (Note 4) is added dropwise to the stirred solution over 30 min. After the addition, the reaction mixture is warmed to room temperature and stirred overnight. The reaction is quenched with 80 mL of aqueous saturated sodium bicarbonate, the phases are separated and the aqueous phase is extracted with dichloromethane (2 x 200 mL). The combined organic extracts are washed with brine (2 x 100 mL) and dried over anhydrous magnesium sulfate. After filtration, the solvent is removed under reduced pressure to give a yellow oil. Purification by flash column chromatography (140 g of silica gel) (Note 5) and eluting with 25% ethyl acetate in hexanes gives a white solid that can be recrystallized from ethyl acetate/hexanes to yield 1,3,5-O-tribenzoyl-2-O-[(3-trifluoromethyl)benzoyl]- α -D-ribofuranose (5.62 g, 82% yield) as white crystals, mp 109-111°C (lit.² mp 102°C) (Note 6).

B. *2,4-Bis(trimethylsilyloxy)-5-methylpyrimidine*. In an oven-dried, 1-L, round-bottomed flask is placed thymine (12.6 g, 0.1 mol) (Note 1) and chlorotrimethylsilane (Note 7) in 300 mL of benzene (Note 8) under an argon atmosphere. To the stirred suspension is added triethylamine (20.2 g, 0.2 mol) (Note 9) dropwise via a dropping funnel over 1 hr. After the addition is complete, the reaction is stirred overnight. The precipitated triethylammonium chloride and unreacted thymine are removed by suction filtration (Note 10) and the solid is washed with dry benzene (2 x 30 mL). The solvent is then removed with a rotary evaporator. The resulting viscous oil is distilled

under reduced pressure (bp 94-97°C at 9 mm, lit.³ bp 124°C at 14 mm) to give 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine (24.0 g, 89% yield). The product solidifies upon standing overnight, mp 73-75°C (lit.³ mp 63-65°C) (Note 11).

C. *3',5'-Di-O-benzoyl-2'-O-[(3-trifluoromethyl)benzoyl]-5-methyluridine*. In an oven-dried, 250-mL, round-bottomed flask equipped with a magnetic stir bar and a rubber septum is placed 1,3,5-tri-O-benzoyl-2-O-[(3-trifluoromethyl)benzoyl]- α -D-ribofuranose (5.6 g, 8.8 mmol) and 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine (2.16 g, 7.1 mmol) in 100 mL of acetonitrile (Note 12). At this stage, the reaction may appear as a white suspension (Note 13). The stirred reaction mixture is cooled to 0°C and tin(IV) chloride (13.75 g, 52.8 mmol) (Note 14) is added dropwise over 15 min with vigorous stirring. Upon addition of tin(IV) chloride, the reaction becomes homogeneous. The reaction mixture is warmed to room temperature and stirred for 6 hr. The reaction is then quenched by pouring the mixture into a 1-L separatory funnel containing 250 mL of aqueous saturated sodium bicarbonate and 200 g of ice. Upon quenching the reaction, voluminous white precipitates appear. Ethyl acetate (200 mL) is added, the separatory funnel is cautiously swirled, and the layers are allowed to separate. The aqueous layer, which now appears milky white, is further extracted with ethyl acetate (2 x 100 mL). The combined extracts are washed with brine (2 x 200 mL) and dried over anhydrous sodium sulfate. After filtration, the solvent is removed under reduced pressure to give a yellow oil. Purification by flash column chromatography (100 g of silica gel) (Note 5) eluting with 25% ethyl acetate in hexanes gives 3',5'-di-O-benzoyl-2'-O-[(3-trifluoromethyl)benzoyl]-5-methyluridine as a white solid (3.52 g, 62% yield), mp 92-95°C (Notes 15, 16).

D. *3',5'-Di-O-benzoylthymidine*. In a 500-mL photochemical reaction vessel, (Note 17) equipped with a magnetic stir bar, is placed 3',5'-di-O-benzoyl-2'-O-[(3-trifluoromethyl)benzoyl]-5-methyluridine (3.82 g, 6.0 mmol), magnesium perchlorate hexahydrate (0.46 g, 1.4 mmol) (Note 1) and 9-ethyl-3,6-dimethylcarbazole (200 mg,

0.9 mmol; for preparation see: Buck, J. P.; Park, M.; Wang, Z.; Prudhomme, D. R.; Rizzo, C. J. *Org. Synth.* **1999**, 77, 153) in 500 mL of 9:1 2-propanol/water (Note 18). The solution is degassed by bubbling argon through the solution for 1 hr using a syringe needle. The photochemical immersion well, equipped with a Pyrex filter is fitted into the reaction vessel and made air tight by lightly greasing the ground glass joints; an argon atmosphere is maintained. The reaction is cooled with an ice bath (Note 19) and photolyzed with a Hanovia 450W, medium pressure mercury lamp through a Pyrex filter for 1 hr (Note 20). The reaction mixture is transferred to a 1-L flask and the solvent is removed with a rotary evaporator. The residue is dissolved in ethyl acetate (150 mL), washed with aqueous saturated sodium bicarbonate (2 x 30 mL), then brine (30 mL), and the organic phase is dried over magnesium sulfate. After filtration, the solvent is removed under reduced pressure to give a yellow oil. Purification by flash column chromatography (150 g of silica gel) (Note 5) eluting with 50% ethyl acetate in hexanes gives 3',5'-di-O-benzoylthymidine (1.43 g, 53% yield), mp 195-196°C (lit.⁴ mp 194-195°C) (Note 21), and 5'-O-benzoyl-3'-deoxythymidine (0.32 g, 16% yield), mp 71-74°C (lit.⁵ mp 57-59°C) (Note 22), and recovered starting material (0.41 g, 11% yield) (Note 23).

2. Notes

1. The ribofuranose was obtained from Aldrich Chemical Company, Inc., and used as received.
2. 2,6-Lutidine (99%) was obtained from Aldrich Chemical Company, Inc., in a Sure/Seal bottle and used as received.
3. Dichloromethane was freshly distilled from calcium hydride.
4. 3-(Trifluoromethyl)benzoyl chloride was obtained from Acros Chemicals or Aldrich Chemical Company, Inc., and used as received.

5. Silica gel (32-63 μm) was obtained from Fisher Scientific Company.

6. The physical properties are as follows: $[\alpha]_D^{21} +89.5^\circ$ (CHCl_3 , c 0.1); IR (KBr) cm^{-1} : 1730; ^1H NMR (CDCl_3) δ : 4.71 (ABX, 2 H, $J_{AB} = 12.1$, $J_{AX} = 3.5$, $J_{BX} = 3.1$, $\Delta\nu_{AB} = 32.6$), 4.93 (m, 1 H), 5.79 (dd, 1 H, $J = 6.5$, 4.4), 5.88 (dd, 1 H, $J = 6.5$, 2.1), 6.91 (d, 1 H, $J = 4.3$), 7.31-7.61 (m, 10 H), 7.72 (d, 1 H, $J = 4.3$), 8.0-8.11 (m, 8 H); ^{13}C NMR (CDCl_3) δ : 64.0 (t), 70.7 (d), 71.5 (d), 82.8 (d), 94.9 (d), 126.3, 126.4, 128.4, 128.5, 128.6, 128.9, 129.2, 129.3, 129.5, 129.7, 129.8, 130.0, 133.0, 133.4, 133.6, 133.7, 163.5, 165.1, 165.6, 166.0 (s), several aromatic signals were not resolved; exact mass calcd. for $\text{C}_{34}\text{H}_{25}\text{F}_2\text{O}_9$ ($\text{M}^+ - \text{F}$) m/z 615.1480. found m/z 615.1473. Anal. Calcd for $\text{C}_{34}\text{H}_{25}\text{F}_3\text{O}_9$: C, 64.34; H, 3.97. Found: C, 63.90; H, 3.97.

7. Chlorotrimethylsilane (99+%) was obtained from Aldrich Chemical Company, Inc., in a Sure/Seal bottle and used as received or distilled from calcium hydride just prior to use.

8. Benzene was freshly distilled from sodium.

9. Triethylamine (99+%) was obtained from Aldrich Chemical Company, Inc., and was freshly distilled from calcium hydride.

10. A plastic drying tube filled with Drierite was placed between the filter and the aspirator.

11. The product was stored under argon in a desiccator and appears to be stable for months. This material exhibited the following spectral characteristics: ^1H NMR (C_6D_6) δ : 0.3 (s, 9 H), 0.4 (s, 9 H), 1.8 (s, 3 H), 7.8 (s, 1 H); exact mass calcd. for $\text{C}_{11}\text{H}_{19}\text{N}_2\text{O}_2\text{Si}_2$ ($\text{M}^+ - \text{CH}_3$) m/z 255.0918. found m/z 255.0963.

12. Anhydrous acetonitrile was obtained from Aldrich Chemical Company, Inc. in a Sure/Seal bottle and used as received.

13. The white insoluble material is partially hydrolyzed bis-TMS-thymine. The degree to which this suspension forms depends on the purity of the bis-TMS-thymine and the water content of the flask and solvents.

14. Neat tin(IV) chloride (99%) was obtained from Aldrich Chemical Company, Inc. in a Sure/Seal bottle and used as received.

15. The physical properties are as follows: $[\alpha]_D^{21} -78^\circ$ (CHCl_3 , c 0.1); ^1H NMR (CDCl_3) δ : 1.54 (s, 3 H), 4.65 (m, 1 H), 4.70 (ABX, 2 H, $J_{AB} = 12.3$, $J_{AX} = 2.6$, $J_{BX} = 3.5$, $\Delta\nu_{AB} = 69.5$), 5.75 (t, 1 H, $J = 6.1$), 5.84 (dd, 1 H, $J = 3.8$, 6.0), 6.33 (d, 1 H, $J = 6.1$), 7.33-7.63 (m, 8 H), 7.93 (d, 2 H, $J = 7.3$), 7.99-8.17 (m, 4 H), 8.78 (br s, 1 H); ^{13}C NMR (CDCl_3) δ : 12.4, 64.2, 71.6, 74.0, 80.8, 87.3, 112.5, 127.0, 128.7, 128.9, 129.1, 129.4, 129.6, 129.9, 130.0, 130.6, 133.4, 134.0, 135.1, 150.6, 163.7, 164.4, 165.7, 166.2; IR (KBr) cm^{-1} : 3373, 3276, 3074, 1725, 1619, 1452, 1267, 1128, 1095, 713. Anal. Calcd for $\text{C}_{32}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_9$: C, 60.17; H, 3.95. Found: C, 60.26; H, 4.06.

16. The submitters report an 82% yield for this reaction. The checkers recovered 0.5 g (9%) of starting material (mp 108-110°C) after recrystallization of material from early fractions of the column.

17. The submitters purchased the reaction vessel from Ace Glass, Inc. (Catalog # 7841-15) and used a quartz immersion well purchased from Ace Glass, Inc. (Catalog # 7858-08) with a Pyrex filter and a Hanovia medium pressure, 450 W mercury lamp (Ace Glass, Inc. Catalog #7875). The checkers used the same apparatus except with a jacketed Pyrex immersion well in place of the quartz immersion well with a Pyrex filter.

18. The solvent was previously degassed by bubbling UHP argon through the solvent for 30 min using a gas sparger. HPLC grade 2-propanol was obtained from Aldrich Chemical Company, Inc., and used as received. The submitters used deionized water and the checkers used HPLC grade water from Aldrich Chemical Company, Inc.

19. The reaction assembly was immersed in a 5-gallon bucket of ice water. The reaction temperature was monitored and never went higher than 20°C. The checkers

cooled the immersion well with recirculating water chilled to 10°C and used a 9-L bucket of ice water, and the internal temperature never went higher than 15°C.

20. The rate of reaction is highly variable depending on the UV source. The reaction is easily monitored by TLC on silica gel using ethyl acetate-hexane (1:1) as the eluent and p-anisaldehyde stain. The R_f values and staining colors of starting materials and products follow: 9-ethyl-3,6-dimethylcarbazole: R_f = 0.95 (gray); 3',5'-di-O-benzoyl-2'-O-[(3-trifluoromethyl)benzoyl]-5-methyluridine: R_f = 0.75 (pink-purple); 5'-O-benzoyl-3'-deoxythymidine: R_f = 0.55 (aqua blue); 3',5'-di-O-benzoylthymidine: R_f = 0.30 (brown-black).

21. The submitters indicate that synthetic 3',5'-di-O-benzoylthymidine was identical in all respects to an authentic sample prepared by the benzylation of thymidine: IR (KBr) cm^{-1} : 1695; ^1H NMR (CDCl_3) δ : 1.62 (s, 3 H), 2.35-2.37 (m, 1 H), 2.67-2.73 (m, 1 H), 4.54 (d, 1 H, J = 2.0), 4.75 (ABX, 2 H, J_{AB} = 12.3, J_{AX} = 3.0, J_{BX} = 2.9, $\Delta\nu_{AB}$ = 36.7), 5.66 (d, 1 H, J = 4.5), 6.47 (d, 1 H, J = 8.7, 5.6), 7.46-7.51 (m, 5 H), 7.60-7.65 (m, 2 H), 8.03-8.09 (m, 4 H), 8.50 (br s, 1 H); ^{13}C NMR (CDCl_3) δ : 12.7 (q), 38.0 (t), 64.3 (t), 75.0 (d), 82.7 (d), 84.9 (d), 111.7 (s), 128.6 (d), 128.8 (d), 129.0 (s), 129.3 (s), 129.5 (d), 129.8 (d), 133.7 (d, 2C), 134.4 (d), 150.1 (s), 163.2 (s), 166.0 (s), 166.1 (s). Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_7$: C, 63.98; H, 4.93. Found: C, 64.07; H, 4.96.

22. Synthetic 5'-O-benzoyl-3'-deoxythymidine was identical in all respects to an authentic sample prepared by the benzylation of 3'-deoxythymidine: IR (KBr) cm^{-1} : 1694; ^1H NMR (CDCl_3) δ : 1.70 (d, 3 H, J = 0.9), 1.76-2.21 (m, 3 H), 2.44-2.51 (m, 1 H), 4.40-4.50 (m, 1 H), 4.53 (dd, 1 H, J = 12.2, 4.6), 4.65 (dd, 1 H, J = 12.2, 2.8), 6.1 (dd, 1 H, J = 6.4, 4.2), 7.35 (s, 1 H), 7.45 (t, 2 H, J = 7.5), 7.60 (t, 1 H, J = 7.4), 8.03 (d, 2 H, J = 7.1), 8.98 (br s, 1 H); ^{13}C NMR (CDCl_3) δ : 12.4, 26.0, 32.3, 65.3, 78.4, 86.1, 110.7, 128.7, 129.6, 133.4, 133.5, 135.1, 150.3, 163.8, 166.0.

23. In one experiment, the checkers obtained 30%, 53%, and 1% of starting material (SM), monodeoxygenation product (MD) and dideoxygenation product (DD),

respectively, after 7 hr of irradiation. In a second experiment, they obtained 3%, 57%, and 5% of SM, MD, and DD, respectively, after 10 hr of irradiation. The checkers also recovered 110 mg (55%) of 9-ethyl-3,6-dimethylcarbazole (mp 56-58°C) from early fractions of the column.

Waste Disposal Information

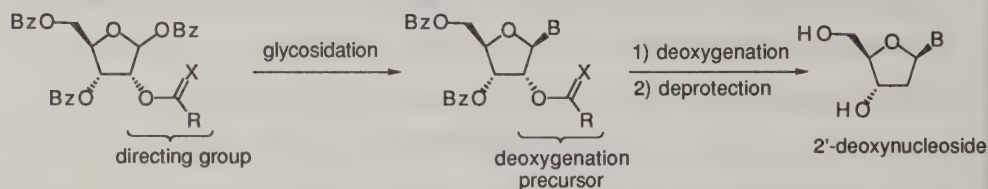
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Nucleosides and nucleoside analogs are a clinically proven class of medicinal agents possessing antiviral and anticancer activity.⁶ The currently used sequence for the de novo synthesis of nucleosides involves the reaction of ribose tetraester with the appropriate silylated base under Lewis acid conditions (Vorbrüggen glycosylation).^{6,7} Presumably, reaction of ribose tetraester with Lewis acids give an oxacarbenium ion intermediate. Neighboring group participation of the α -C₂-ester group directs glycosylation exclusively to the desired β -face. In the absence of a directing C₂-group, mixtures of anomers are usually obtained. Robins developed an efficient procedure for the conversion of ribonucleosides to 2'-deoxyribonucleosides that relies on the simultaneous protection of the 3'- and 5'-hydroxyl groups with a bifunctional silylating reagent. The 2'-position is then deoxygenated via tin hydride reduction of the corresponding 2'-phenoxythionocarbonate.⁸

The strategy here was to develop a ribose glycosylation precursor in which the α -C₂-ester could serve as both a directing group for Vorbrüggen glycosylation and a deoxygenation precursor. This strategy was previously employed by Benner for the

synthesis of potential antisense nucleosides with modified backbones.⁹ In this work, a *m*-(trifluoromethyl)benzoyl group was used as the directing group/deoxygenation precursor. The submitters subsequently developed this strategy into a general method for the synthesis of β -2'-deoxyribonucleosides.¹⁰ The selective deoxygenation of the 2'-*m*-(trifluoromethyl)benzoyl group is achieved via a photoinduced electron-transfer (PET) mechanism using stoichiometric 9-methylcarbazole (MCZ) as the electron donor.¹¹



The submitters recently reported the development of 9-ethyl-3,6-dimethylcarbazole (DMECZ) (see also accompanying procedure) as a donor that can be used in 10-20 mol %.¹² In their original report,¹⁰ PET deoxygenation required 6-8 hr with stoichiometric MCZ at a substrate concentration of 1.4 mM. At higher substrate concentrations, the efficiency of PET deoxygenation dramatically decreased with MCZ. With 10-20 mol % of DMECZ as the donor, the deoxygenation of 3',5'-di-*O*-benzoyl-2'-*O*-[(3-trifluoromethyl)benzoyl]-5-methyluridine required 1-10 hr at a much higher substrate concentration, making the current procedure efficient and practical. DMECZ also shows improved reactivity and is able to deoxygenate benzoyl groups as well as *m*-(trifluoromethyl)benzoyl groups. This improved reactivity allowed the submitters to apply this strategy to the synthesis of α -2'-deoxyribonucleosides,¹³ β -3'-deoxyribonucleosides and β -2',3'-dideoxyribonucleosides (Table).

Acknowledgment: This work was supported by Grant #DHP-172 from the American Cancer Society.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- 3',5'-Di-O-benzoylthymidine: Thymidine, 3',5'-dibenzoate (9); (35898-30-7)
- 1,3,5-O-Tribenzoyl-2-O[(3-trifluoromethyl)benzoyl]- α -D-ribofuranose:
 α -D-Ribofuranose, 1,3,5-tribenzoate 2-[3-(trifluoromethyl)benzoate] (13); (145828-13-3)
- 1,3,5-Tri-O-benzoyl- α -D-ribofuranose: Aldrich: α -D-Ribofuranose 1,3,5-tribenzoate: Ribofuranose, 1,3,5-tribenzoate, α -D- (8); α -D-Ribofuranose, 1,3,5-tribenzoate (9); (22224-41-5)
- 2,6-Lutidine (8); Pyridine, 2,6-dimethyl- (9); (108-48-5)
- 3-(Trifluoromethyl)benzoyl chloride: m-Toluoyl chloride, α,α,α -trifluoro- (8); Benzoyl chloride, 3-(trifluoromethyl)- (9); (2251-65-2)
- 2,4-Bis(trimethylsilyloxy)-5-methylpyrimidine: Pyrimidine, 5-methyl-2,4-bis(trimethylsiloxy)- (8); Pyrimidine, 5-methyl-2,4-bis[(trimethylsilyl)oxy]- (9); (7288-28-0)
- Thymine (8); 2,4(1H,3H)-Pyrimidinedione, 5-methyl- (9); (65-71-4)
- Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)
- Benzene: CANCER SUSPECT AGENT (8,9); (71-43-2)
- Trimethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)
- 3',5'-Di-O-benzoyl-2'-O[(3-trifluoromethyl)benzoyl]-5-methyluridine: Uridine, 5-methyl-, 3',5'-dibenzoate 2'-[3-(trifluoromethyl)benzoate] (13); (182004-59-7)
- Acetonitrile: TOXIC (8,9); (75-05-8)
- Tin(IV) chloride: Tin chloride (8); Stannane, tetrachloro- (9); (7646-78-8)
- Magnesium perchlorate hexahydrate: Perchloric acid, magnesium salt, hexahydrate (8,9); (13446-19-0)

9-Ethyl-3,6-dimethylcarbazole: 9H-Carbazole, 9-ethyl-3,6-dimethyl- (9); (51545-42-7)

5'-O-Benzoyl-3'-deoxythymidine: Thymidine, 3'-deoxy-, 5'-benzoate (12);

(122621-07-2)

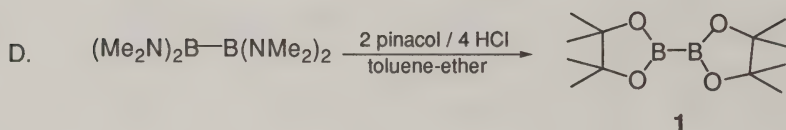
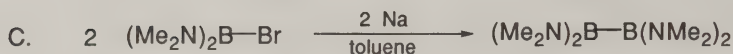
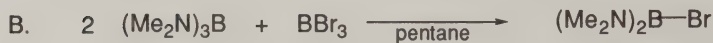
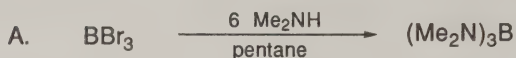
TABLE
SYNTHESIS OF DEOXYRIBONUCLEOSIDES VIA PET DEOXYGENATION

Substrate (Ar= m- CF ₃ C ₆ H ₄ -)	Donor	Product	Yield
	MCZ		70%
	MCZ		53%
	MCZ		44%
	DMECZ		70%
	DMECZ		58%
	DMCZ		73%
	DMECZ		69%

Substrate (Ar= m- CF ₃ C ₆ H ₄ -)	Donor	Product	Yield
	DMECZ		80%
	DMECZ		81%
	DMECZ		76%
	DMECZ		60%
	DMECZ		71%
	DMECZ		65%
	DMECZ		68%

BIS(PINACOLATO)DIBORON

(2,2'-Bi-1,3,2-dioxaborolane, 4,4,4',4',5,5,5',5'-octamethyl-)



Submitted by Tatsuo Ishiyama, Miki Murata, Taka-aki Ahiko, and Norio Miyaura.¹

Checked by Glenn C. Micalizio and William R. Roush.

1. Procedure

Caution! All the operations should be carried out in a well-ventilated hood, since bromoborane derivatives fume in air and are rapidly hydrolyzed with the evolution of considerable heat.

A. Tris(dimethylamino)borane (Note 1). A 2-L, three-necked flask equipped with a mechanical stirrer, dropping funnel, and a dry ice-cooled reflux condenser connected to a nitrogen source and a bubbler is flushed with nitrogen (Note 2). The flask is charged with 800 mL of pentane (Note 3) and 218 g (4.84 mol) of dimethylamine (Note 4), and cooled to ca. -30°C with a dry ice-methanol bath. A

solution of 201 g (0.801 mol) of boron tribromide (Note 5) in 400 mL of pentane is added dropwise through the addition funnel over 3 hr to the vigorously stirred solution while maintaining the bath-temperature at -20°C to -10°C (Note 6). As soon as the addition is begun, a white precipitate of dimethylamine hydrobromide appears. The temperature is allowed to rise to ambient temperature without removing the cooling bath, and the slurry is stirred for 16 hr at room temperature. The precipitate is removed by filtration through a Celite pad on a glass-fritted filter funnel (Note 7). The flask and filter cake are rinsed three times with 60 mL of pentane. The pentane solution is distilled to give 92.7 g (81%) of tris(dimethylamino)borane as a colorless liquid, bp 44-45°C (12 mm), lit.² bp 39°C (10 mm) (Notes 8, 9).

B. Bromobis(dimethylamino)borane. A 500-mL, two-necked flask equipped with a magnetic stirring bar, dropping funnel, and a distillation apparatus connected to a nitrogen source and a bubbler is flushed with nitrogen (Note 2). The flask is charged with 100 mL of pentane (Note 3) and 92.7 g (0.648 mol) of tris(dimethylamino)borane, and cooled to -40°C (external bath temperature) with a dry ice-methanol bath. A solution of 81.3 g (0.324 mol) of boron tribromide (Note 5) in 80 mL of pentane is added dropwise to the stirred solution over a period of 1.5 hr maintaining the external bath temperature at -40°C. The cooling bath is removed and the solution is stirred at room temperature for 30 min. Distillation affords 172.8 g (99%) of bromobis(dimethylamino)borane as a colorless liquid, bp 56-58°C (12 mm), lit.³ bp 20-28°C (0.5 mm) (Note 10).

C. Tetrakis(dimethylamino)diboron. A 500-mL, three-necked flask equipped with an airtight mechanical stirrer, a dropping funnel, and a reflux condenser connected to a nitrogen source and a bubbler is flushed with nitrogen (Note 2). The flask is charged with 78 mL of toluene (Note 11) and 22.3 g (0.97 g-atom) of sodium. The mixture is brought to reflux with an oil bath and the sodium is finely pulverized by vigorous stirring. A solution of 135.6 g (0.758 mol) of bromobis(dimethylamino)borane

in 55 mL of toluene is added dropwise at a rate sufficient to maintain a gentle reflux over 45 min. Shortly after the addition is begun, a deep-blue precipitate appears (Note 12). The suspension is heated at reflux for an additional 2.5 hr. The slurry is cooled to room temperature, and filtered through a Celite pad on a sintered-glass funnel (Note 7). The flask and filter cake are rinsed three times with 50 mL of toluene (Note 13). The yellow filtrate is concentrated under reduced pressure, and the residual oil is distilled under reduced pressure to give 54 g (72%) of tetrakis(dimethylamino)diboron as a colorless liquid, bp 92°C (12 mm), lit.³ bp 55-57°C (2.5 mm) (Note 14).

D. Bis(pinacolato)diboron (1). A 2-L, three-necked flask fitted with a mechanical stirrer, dropping funnel, and a reflux condenser connected to a nitrogen source and a bubbler is flushed with nitrogen (Note 2). To the flask are added 53.7 g (0.271 mol) of tetrakis(dimethylamino)diboron and 510 mL of toluene (Note 11), and then a solution of 64.4 g (0.545 mol) of pinacol (Note 15) in 340 mL of toluene. The flask is immersed in an ice-water bath and a 5.4 M ethereal solution of hydrogen chloride (Note 16) (203 mL, 1.10 mol) is added dropwise during 2 hr. As soon as the addition is started, a white precipitate of dimethylamine hydrochloride appears. The slurry is stirred at room temperature for an additional 4 hr. The precipitate is removed by filtration in a Büchner funnel with suction, and the filtrate is concentrated on a rotary evaporator to give a white solid. The solid is dissolved in ca. 700 mL of pentane and the remaining solid is again removed by filtration. The filtrate is washed three times with 500 mL of water and dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the filtrate is concentrated to ca. 150 mL. The flask is heated to dissolve the resulting precipitate, allowed to cool to room temperature, and then thoroughly chilled in a freezer (-30°C). The first crop is collected by filtration and washed twice with 30 mL of cold pentane. The mother liquor is again concentrated to give another crop of crystals. The procedure is repeated two additional times. The

combined crystals are dried under reduced pressure (0.1 mm) for 16 hr at room temperature to give 54.3 g (79%) of **1** as colorless plates, mp 138°C, lit.⁴ mp 138°C (Notes 17, 18).

2. Notes

1. Tris(dimethylamino)borane is available from Aldrich Chemical Company, Inc. It may also be synthesized from boron trichloride.²

2. All glassware is predried in an oven at 120°C for 1 hr, assembled while hot, and allowed to cool under a stream of nitrogen.

3. Pentane is distilled from lithium aluminum hydride before use.

4. Dimethylamine (bp 6°C) is condensed at -78°C into a 500-mL flask fitted with an inlet tube and a nitrogen bubbler. The quantity of dimethylamine in the flask is determined by periodic weighing. Dimethylamine is either taken from a cylinder (Aldrich Chemical Company, Inc.) or from a mixture of an aqueous 50% solution of dimethylamine and potassium hydroxide.⁵ Checkers condensed dimethylamine directly into the 2-L reaction vessel with periodic weighing.

5. Boron tribromide was purchased from Wako Pure Chemical Industries, Ltd. or Aldrich Chemical Company, Inc., and used without further purification.

6. *Caution! Addition at lower than -20°C leads to a violent reaction during warming up to -10-0°C.*

7. A large filter area is recommended. A 1-cm layer of Celite is pressed on a sintered-glass funnel (6 cm x 17 cm). The Celite is dried in an oven at 120°C for 12 hr. A 6-mm Teflon tube is used to connect the flask and the filter funnel through the septa, and the stirred slurry is then transferred to the funnel with the aid of nitrogen pressure. Inner pressure of the receiver flask and the funnel is leaked through oil bubblers. The

checkers had difficulty with the filter clogging, so they used a Schlenk filter apparatus instead.

8. Tris(dimethylamino)borane is moisture sensitive. ^1H NMR (CDCl_3) δ : 2.52 (s, 18 H).

9. The checkers obtained a 63% yield of tris(dimethylamino)borane. The checkers obtained bp 57°C (11 mm).

10. Bromobis(dimethylamino)borane is moisture sensitive and fumes in air: ^1H NMR (CDCl_3) δ : 2.75 (s, 12 H). The checkers obtained a 96% yield of material with bp 71°C (13 mm).

11. Toluene is distilled from molten sodium before use.

12. The checkers observed an induction period of approximately 20 min followed by a vigorous exotherm. It was only after this exotherm occurred that any blue precipitate was observed in the reaction vessel.

13. The residual solid containing unreacted sodium is carefully treated with ethanol.

14. Tetrakis(dimethylamino)diboron is moisture sensitive. ^1H NMR (CDCl_3) δ : 2.67 (s, 24 H). The checkers observed an unidentified impurity in the ^1H NMR spectrum (δ 2.51, s). The checkers also obtained a slightly better yield (72%) than reported by the submitters (67%) when a freshly opened bottle of sodium was used in this experiment.

15. Pinacol was purchased from Tokyo Kasei Kogyo Co., Ltd. or Aldrich Chemical Company, Inc., and used without further purification.

16. An ethereal solution of hydrogen chloride is titrated with 0.1 M sodium hydroxide before use.

17. The submitters obtained a 91% yield of bis(pinacolato)diboron.

18. Crystalline bis(pinacolato)diboron can be handled in air and stored in a capped bottle. The physical properties are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 1.25 (s, 24 H); ^{11}B NMR (128.3 MHz, toluene) δ 30.61 ($\text{BF}_3\cdot\text{Et}_2\text{O}$ as external reference, δ 0.00); ^{13}C NMR (100 MHz, CDCl_3) δ : 83.4, 24.9; IR (KBr) cm^{-1} : 2978, 2930, 1372, 1289, 1189, 1177, 1127, 960, 850, 744, 660, 547; high resolution mass spectrum, calcd for $\text{C}_{12}\text{H}_{24}\text{B}_2\text{O}_4$ [M^+], 254.1861, found 254.1867. Anal. Calcd. for $\text{C}_{12}\text{H}_{24}\text{B}_2\text{O}_4$; C, 56.76; H, 9.53. Found: C, 56.66; H, 9.50.

Bis(pinacolato)diboron is now commercially available from Lancaster Synthesis Ltd., Callery Chemical Co., Aldrich Chemical Company, Inc., and Frontier Scientific Inc.

Waste Disposal Information

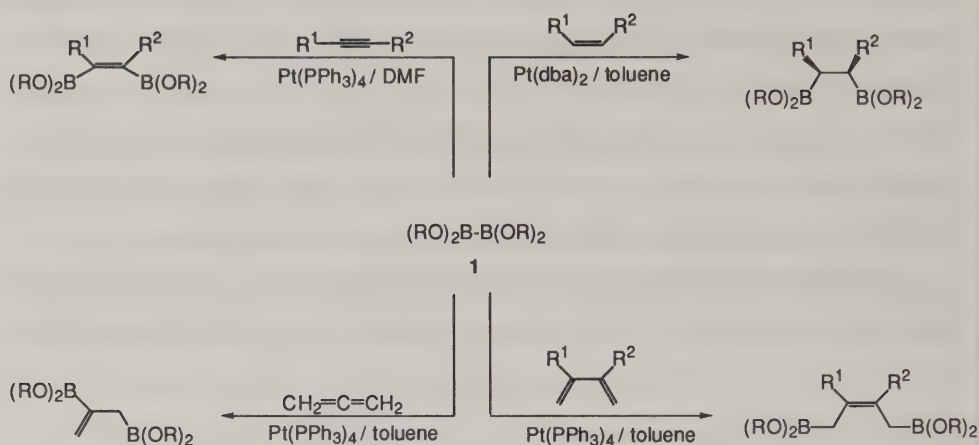
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

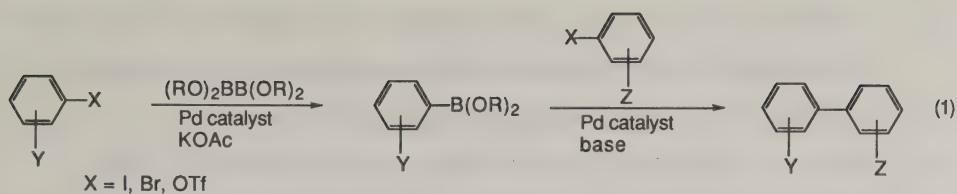
This method is an adaption of the U. S. Borax Research group's procedure³ that illustrates a practical and efficient method for the synthesis of tetra(alkoxo)diborons. Several (alkoxo)diborons, such as tetra(methoxo)-,³ bis(catecholato)-,⁶ and bis(pinacolato)diboron⁴ (**1**), are synthesized from tetrakis(dimethylamino)diboron. The diborons are excellent reagents for the synthesis of various organoboronic esters via the transition metal-catalyzed addition and cross-coupling reactions.⁷⁻¹⁵

The platinum(0) complexes catalyze the addition of **1** to unsaturated hydrocarbons (Scheme 1). The addition to alkynes,⁷ alkenes,⁸ 1,3-dienes,⁹ or allenes¹⁰ stereoselectively provides cis-addition products.

Scheme 1

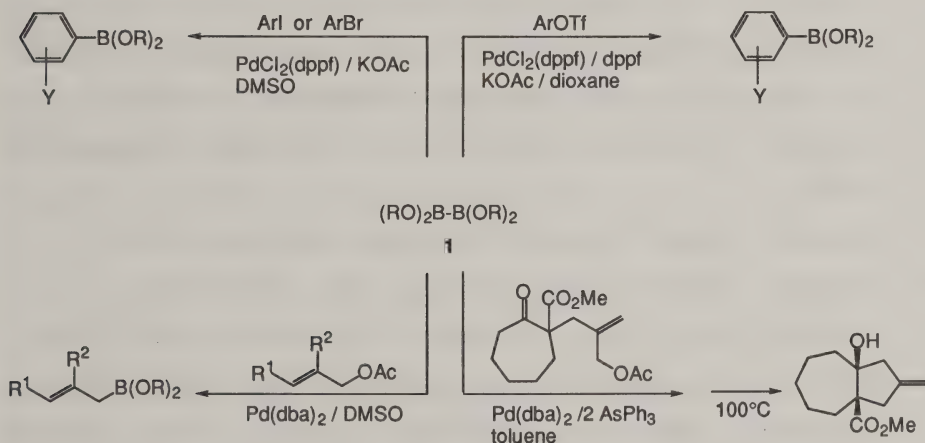


The cross-coupling reaction of **1** with palladium catalyst provides a convenient method for the synthesis of organoboronic esters from organic electrophiles (Scheme 2). Aromatic halides¹¹ and triflates¹² couple with **1** in the presence of $PdCl_2(dppf)$ and potassium acetate (KOAc) to give arylboronates in high yields. The procedure has a wider application over the conventional synthesis based on the addition of aryllithium or Grignard reagents to trialkyl borates, because the reaction tolerates various functional groups, e.g., $-CO_2Me$, $-COMe$, $-CN$, and $-NO_2$. Arylboronic acids and esters have been used for the synthesis of biaryls via the palladium-catalyzed cross-coupling reaction with aryl electrophiles. The use of diboron allows sequential, double cross-couplings in the same flask to provide biaryls (eq. 1).^{12, 13}



Coupling with allyl acetates gives allyl boronates,¹⁴ which exhibit a high diastereoselectivity in the intramolecular allyl boration of carbonyl compounds¹⁵ (Scheme 2).

Scheme 2



1. Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Bis(pinacolato)diboron: 2,2'-Bi-1,3,2-dioxaborolane, 4,4,4',4',5,5,5',5'-octamethyl- (10); (73183-34-3)

Dimethylamine (8); Methanamine, N-methyl- (9); (124-40-3)

Tris(dimethylamino)borane: Borane, tris(dimethylamino)- (8); Boranetriamine, hexamethyl- (9); (4375-83-1)

Boron tribromide: Boron bromide (8); Borane, tribromo- (9); (10294-33-4)

Bromobis(dimethylamino)borane: Borane, bromobis(dimethylamino)- (8);

Boranediamine, 1-bromo-N,N,N',N'-tetramethyl- (9); (6990-27-8)

Tetrakis(dimethylamino)diboron: Diborane(4), tetrakis(dimethylamino)- (8);

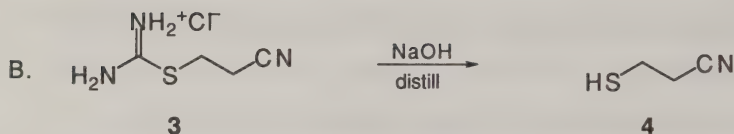
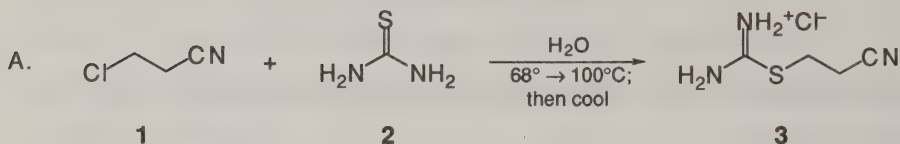
Diborane(4)tetramine, octamethyl- (9); (1630-79-1)

Sodium (8,9); (7440-23-5)

Pinacol: 2,3,-Butanediol, 2,3-dimethyl- (8,9); (76-09-5)

β -MERCAPTOPROPIONITRILE (2-CYANOETHANETHIOL)

(Propanenitrile, 3-mercapto-)



Submitted by R. Eric Gerber, Carlos Hasbun, Larisa G. Dubenko, Mei Fong King, and Donald E. Bierer.¹

Checked by Joseph Barbosa and Amos B. Smith, III.

1. Procedure

Caution: The procedure should be carried out in a well-ventilated hood because of the extreme stench of the mercaptan products. All glassware used in the procedure should be soaked in a bleach solution prior to removal from the hood.

A. *2-Cyanoethylthiuronium hydrochloride (3).* To a 5-L, flanged-top, spherical Morton flask equipped with a supporting clamp (Note 1) are added water (380 mL), thiourea (575 g, 7.53 mol), and 3-chloropropionitrile (500 g, 5.58 mol) (Note 2). The flask is equipped with a three-necked (with thermometer inlet) flanged-top, mechanical stirring rod (600 mm) with Teflon paddle (110 mm), temperature probe, reflux condenser, gas bubbler, and 5-L heating mantle. The reaction mixture is slowly

heated to 68°C over a 30-min period under nitrogen and maintained at 68-70°C for 1 hr (Note 3). After 1 hr, the temperature of the reaction mixture is increased over a 15-min period to 100°C and maintained at 100-101°C for 2 hr (Note 4). After 2 hr, the heating mantle is replaced with a large ice-salt bath, and the reaction mixture is cooled with stirring to 45°C. When the internal temperature of the reaction mixture reaches 45°C, stirring is stopped, the cooling process is continued, and the product is allowed to crystallize (Note 5). Cold acetone (2 L) is added and the solid is broken up with a spatula and homogenized (Note 6). The solid is collected using a 160 x 160-mm medium-fritted funnel and washed with 4 L of cold acetone, stirring with the spatula during the filtration process. The solid is then washed with 2 L of ether and air dried. Final drying in a vacuum oven at room temperature affords 693.7 g (75.0%) of the title compound as a white solid, mp 161.5-162.5°C (Notes 7 and 8). The filtrate is placed in a freezer (4°C) for two days. The crystallized product is collected by vacuum filtration, washed with ether (2 x 1 L), air dried, and then dried under vacuum to afford an additional 75.8 g (8.2%) of the title compound, mp 162.5-163.5°C (Note 9).

B. 2-Cyanoethanethiol (4). To a 3-L, three-necked, round-bottomed flask equipped with a supporting clamp are added thiuronium salt **3** (369.8 g, 2.23 mol) and water (470 mL) (Note 10). The flask is equipped with a mechanical stirring rod (600 mm) with Teflon paddle (110 mm), temperature probe, gas bubbler, a Teflon tube that extends into the reaction mixture for bubbling nitrogen gas, and a 3-L heating mantle. The reaction mixture is purged with nitrogen by rapidly bubbling nitrogen into the reaction mixture with stirring for 15 min. The Teflon tube is removed, replaced with a 500-mL addition funnel, and then a concentrated solution of sodium hydroxide (NaOH, 11.25 M, 4.24 mol) is slowly added under a nitrogen atmosphere, keeping the internal temperature below 25°C (Note 11). After the addition is complete, the reaction mixture is heated to 45°C over a 10-min period and held at 45-47°C for 45 min (Note 12). The heating mantle is removed and replaced with a large ice-salt bath. After the

reaction mixture has cooled to 20°C, a 6 M solution of H₂SO₄ is slowly added under nitrogen, keeping the internal reaction temperature between 20-25°C, until the pH of the reaction mixture is 6 (Note 13). With rapid bubbling of nitrogen to maintain a nitrogen atmosphere, the addition funnel is removed and commercial anhydrous ether (500 mL) is added to the reaction mixture. The flask is equipped with a one-hole rubber septum into which a Teflon tube (1 m x 4-mm id) is inserted. The mixture is stirred for 1 min, and the layers are allowed to separate. The temperature probe is removed and replaced with a rubber septum. Positive nitrogen pressure is applied to transfer the top ether layer using the Teflon tube into a 4-L Erlenmeyer flask with a 24/40 ground glass joint containing magnesium sulfate (MgSO₄, 375 g) and a nitrogen atmosphere, cracking or removing the rubber septum on the thermometer inlet as needed to control the rate of transfer. This extraction process with ether is repeated four times using 500-mL portions. After the combined ether layers are dried over MgSO₄ under nitrogen, they are filtered through a sintered glass funnel containing MgSO₄ and concentrated using a rotary evaporator to about 500 mL in total volume. The concentrated ether solution is redried over MgSO₄ (125 g, under nitrogen), filtered, and concentrated using the rotary evaporator. The product is transferred into a 250-mL, round-bottomed flask and distilled through a short-path jacketed distillation apparatus (Notes 14 and 15). A forerun (approximately 5 mL) is collected and discarded. The product distilling at 30-32°C (0.08-0.12 mm) is collected, providing 106.6 g (55%) of the title compound as a colorless liquid (Notes 16 - 19).

2. Notes

1. The reaction can be carried out in a normal three-necked 5-L Morton flask. However, product **3** will solidify in the flask making its removal from a three-necked flask tedious. The submitter's experience has shown that use of an open top reactor-

type flask makes subsequent processing of the product much easier. The following glassware from Chemglass were used: reactor flask, CG-1955-03; clamp, CG-1970-01; reaction vessel head, CG-1963-01; air-free gas bubbler, AF-0514-02.

2. Thiourea and 3-chloropropionitrile were purchased from Aldrich Chemical Company, Inc., and used as received. Thiourea and 3-chloropropionitrile from Lancaster Laboratories have also been used with similar results. Old bottles of 3-chloropropionitrile should be distilled before use.

3. Care must be taken to heat the reaction mixture slowly and not above 70°C as the reaction mixture can exotherm above 100°C if heated rapidly to approximately 80°C. After the reaction mixture has reached 68°C, the reaction is self-perpetuating for about 30 min and the heating mantle should be removed. The heating mantle can be replaced periodically as necessary during the 1-hr heating time to maintain the temperature at 68-70°C when the reaction mixture begins to cool below 68°C. It is most convenient to use a soft, hemispherical 5-L GlasCol heating mantle that can be easily removed and replaced by slipping it around the flask without having to adjust the rest of the apparatus.

4. The heating mantle can be removed and replaced (or turned off and on) as necessary during the 2-hr heating time to maintain the temperature at 100-101°C.

5. If stirring is not stopped before the product solidifies, the stirring rod will break. It is best to raise the stirring rod and the temperature probe until they touch the top of the liquid in the flask. This assists the crystallization process and prevents supercooling.

6. The acetone used in the workup was precooled to -20°C for 4 hr prior to use. Once the solid is broken up, the stirrer can be used to homogenize the product.

7. The spectral data for **3** are as follows: ^1H NMR (400 MHz, D_2O) δ : 2.83 (t, 2 H, $J = 6.8$), 3.28 (t, 2 H, $J = 6.8$); ^{13}C NMR (100 MHz, D_2O) δ : 18.0, 26.2, 118.8, 169.5; IR (KBr) cm^{-1} : 3275, 3095, 2710, 2241, 1651, 1441, 1411, 671. The literature^{2,3} mp

for **3** is 163-165°C. Using 3-(trimethylsilyl)propanesulfonic acid, sodium salt as the internal reference for ^1H NMR ($\delta = 0$) and methanol as the internal reference for ^{13}C NMR ($\delta = 49.5$), the checkers obtained the following NMR data: ^1H NMR (500 MHz, D_2O) δ : 3.01 (t, 2 H, $J = 6.7$), 3.47 (t, 2 H, $J = 6.7$); ^{13}C NMR (125 MHz, D_2O) δ : 18.6, 26.9, 119.4, 170.3.

8. Anal. Calcd for $\text{C}_4\text{H}_8\text{ClN}_3\text{S}$: C, 29.00; H, 4.87; N, 25.37; S, 19.36. Found: C, 28.75; H, 4.98; N, 25.51, S, 19.59.

9. Anal. Calcd for $\text{C}_4\text{H}_8\text{ClN}_3\text{S}$: C, 29.00; H, 4.87; N, 25.37; S, 19.36. Found: C, 28.71; H, 4.93; N, 25.62; S, 19.68.

10. The reaction mixture cooled to 12°C upon dissolution of thiuronium salt **3**. The checkers, however, found that complete dissolution of **3** was never achieved and that the internal temperature never fell below 15°C. A water bath (ca. 15°C) was therefore used for added temperature control throughout the addition of the NaOH solution.

11. The 11.25 M NaOH solution (prepared from 169.6 g of NaOH) should be cooled to 20°C prior to use.

12. The temperature should not be allowed to go above 50°C. The heating mantle can be removed and replaced (or turned off and on) as necessary during the heating process to maintain the temperature at 45-47°C.

13. Sulfuric acid (250 mL of 6 M H_2SO_4) was prepared and cooled to 20°C prior to use.

14. Freshly opened cans of anhydrous ether (Fisher) were used in the extraction process. Efficient drying over MgSO_4 (under nitrogen) is needed to avoid excessive loss of product in the forerun as a product/water azeotrope. The one-hole rubber septum used for the transfer process was obtained by using a cork bore of the appropriate size on a 24/40 rubber septum (Aldrich Chemical Company, Inc.). Rotary evaporation to remove the ether was carried out at 200-300 mbar (150-225 mm)

initially to prevent bumping. Final rotary evaporation to remove residual ether prior to distillation was done at 40-50 mbar (30-38 mm).

15. The use of a short path distillation apparatus with minimal joint connections, such as Chemglass CG-1240-06, is preferred. Once the distillation apparatus is assembled, vacuum should be gradually applied to remove any remaining residual ether before heat is applied. The receiving flask (500 mL) is placed in a Dewar flask containing a dry ice bath filled to a level to reach the bottom of the ground glass joint during the collection of **4**. The oil bath temperature during the distillation was kept between 50-60°C. Importantly, the vacuum pressure should be kept between 0.05 and 0.15 mm. Pressures in excess of 0.15 mm will lead to extensive thermal decomposition of product and pressures below 0.05 mm will result in loss of product due to volatility.

16. The spectral data for **4** are as follows: ^1H NMR (400 MHz, CDCl_3) δ : 1.78 (t, 1 H, $J = 8.8$), 2.62 (m, 2 H), 2.70-2.76 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ : 20.2, 22.4, 117.8; IR (CCl_4) cm^{-1} : 2927, 2841, 2565, 2235, 1420, 1287; MS (EI) 87 (M^+). The literature³ bp for **4** is 57-59°C (6 mm).

17. Analysis of 2-cyanoethanethiol by GCMS gave one peak at 87 amu with no detectable amount of dimer. The GCMS analysis was performed on a Hewlett-Packard 5890 Series II gas chromatograph equipped with a 5972 series mass selective detector and an HP-5 30-m x 0.25-mm x 0.25- μm column under the following conditions: injector temp 150°C; detector temp 200°C; oven temp 50°C, 3 min; ramp 15°C/min; final temp 200°C; helium gas flow 1.0 mL/min; $t_R = 6.93$ min. Anal. Calcd for $\text{C}_3\text{H}_5\text{NS}$: C, 41.35; H, 5.78; N, 16.07; S, 36.79. Found: C, 41.40; H, 5.85; N, 16.10; S, 37.03.

18. 3,3'-Dithiobispropionitrile was prepared as a reference standard for GCMS analysis according to the procedure of Johnston and Gallagher and was recrystallized from ether.² Physical data for 3,3'-dithiobispropionitrile (unchecked) are as follows:

mp 48.4-48.8°C (lit.² 49-51°C); ¹H NMR (400 MHz, CDCl₃) δ: 2.82 (m, 2 H), 2.94 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ: 17.8, 33.3, 117.7; IR (KBr) cm⁻¹: 2937, 2239, 1411, 1322, 1266, 1204, 940, 895; MS (EI) 172 (M⁺). The GCMS analysis of 3,3'-dithiobispropionitrile using the above conditions gave one peak at t_R = 17.14 min (172 amu).

19. The submitters routinely stored 2-cyanoethanethiol under argon in a -78°C freezer prior to its use.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. Clorox solutions were used for cleaning reaction glassware.

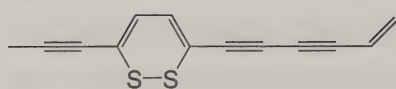
3. Discussion

2-Cyanoethylthiuronium hydrochloride (**3**) has been prepared by Bauer and Welsh from thiourea hydrochloride and acrylonitrile in a 61% yield on a 20-g scale.³ It has also been prepared by Bauer and Welsh³ and by Traut, et al.⁴ using a procedure similar to the one described here on a 17.5-g and 25-g scale, respectively. Both procedures describe the reaction being carried out at refluxing solvent temperatures. These procedures were not reproducible and applicable as described for larger scale preparations. More importantly, they were not safe, as the reaction of thiourea with 2-chloropropionitrile is very exothermic. The procedure described here allows for the safe and reproducible preparation of 2-cyanoethylthiuronium hydrochloride on a scale even 10-fold larger than the one described.

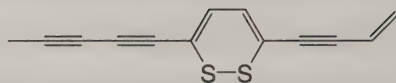
2-Cyanoethanethiol (**4**) has been prepared by Bauer and Welsh³ and by Traut, et al.⁴ using a procedure similar to the one described here. The Bauer and Welsh procedure employed less than a stoichiometric amount of NaOH while the Traut procedure used a small excess of NaOH; both were small scale preparations. The Traut procedure was not reproducible on small or larger scales, as yields never exceeded 35%. The submitters have found that increasing the amount of base during the hydrolysis reaction from that reported leads to an improved, reproducible yield of 2-cyanoethanethiol, provides product of high purity, and is applicable to large scale synthesis.

The 2-cyanoethyl moiety has demonstrated utility as a nitrogen⁵ and sulfur protecting group.^{6,7} 2-Cyanoethanethiol has been used as a thiophile for the preparation of various 3-thio-substituted carbapenems.⁸ More recently it has been used as a protected thiophile for the preparation of 1,2-dithiins, a novel heterocyclic class of compounds related to the biologically active natural products, thiarubrin A and B (Figure 1).^{9,10} The 1,2-dithiin ring system can be constructed in two or three steps using 2-cyanoethanethiol as a key synthetic intermediate. Bis addition of 2-cyanoethanethiol to 2,4-hexadiyne-1,6-diol provides bisthiohexadiene adduct **6**. Optional mono- or bis-silylation of the bisthiohexadiene adduct **6** provides hexadiene adducts **7** and **8**, respectively. Removal of the 2-cyanoethyl moiety by β -elimination followed by oxidation of the intermediate dithioenolate provides dithiins **9**, **10**, and **11** (Scheme 1).¹¹ Desilylation of dithiin **11** using tetrabutylammonium fluoride provides an alternative approach to dithiin **9**. Dithiins **9** and **10** have been used to prepare a variety of 1,2-dithiin analogues, some of which are equipotent and less toxic than their natural product counterparts.^{11,12}

Figure 1



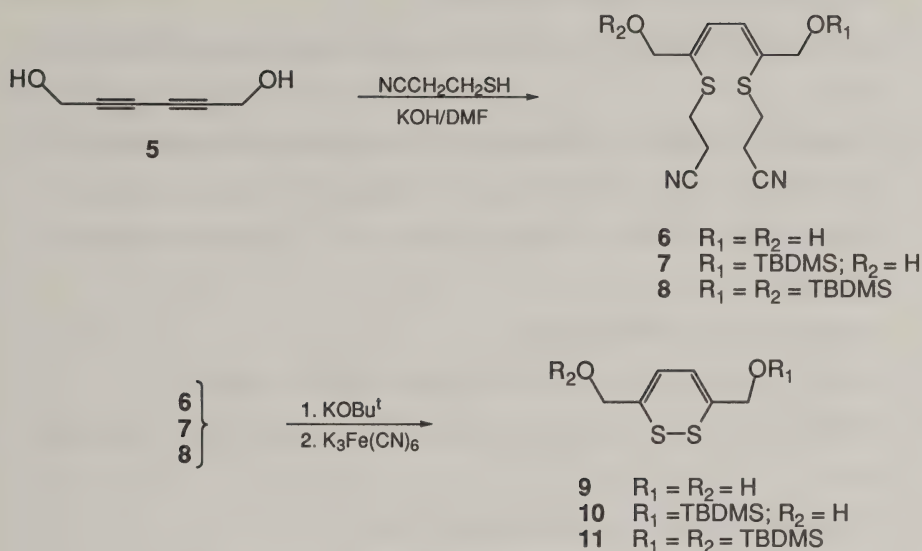
Thiarubrine A



Thiarubrine B

Thioacetate anion is a method of introducing sulfur into organic molecules in a protected form.¹³ The use of 2-cyanoethanethiol as the thiophile for the synthesis of 1,2-dithiins represents an important example where thioacetate fails. Benzylmercaptan^{14,15} and 2-(trimethylsilyl)ethanethiol¹⁶ have been used as protected thiophiles for the preparation of 1,2-dithiins by a similar mechanism. In the case of benzylmercaptan, while the procedure works well for small scale preparations, process considerations hinder its use for larger applications.^{11,16} 2-(Trimethylsilyl)ethanethiol is commercially available and has been used successfully in the total synthesis of thiarubrine A,¹⁶ yet its expense might limit its utility. 2-Cyanoethanethiol offers a practical alternative to both reagents. This preparation of 2-cyanoethanethiol should allow for its continued use as a thiophile and protected thiophile, for use of the 2-cyanoethyl moiety as a valuable protecting group for organic synthesis, and should also allow for further exploration of the 1,2-dithiin class of heterocycles.¹⁷

Scheme 1



1. Medicinal Chemistry Department, Shaman Pharmaceuticals, Inc., 213 East Grand Ave., South San Francisco, CA 94080-4812. Present address for D. E. B.: Bayer Corporation, Department of Chemistry, 400 Morgan Lane, West Haven, CT 06516.
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17. After submission of this procedure the use of tert-butylmercaptan as a thiophile in the synthesis of 1,2-dithiins was reported. See: Koreeda, M.; Wang, Y. *J. Org. Chem.* **1997**, *62*, 446-447.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

β -Mercaptopropionitrile: 2-Cyanoethanethiol: Propionitrile, 3-mercapto- (8);
 Propanenitrile, 3-mercapto- (9); (1001-58-7)
 2-Cyanoethylthiouronium hydrochloride: Carbamimidothioic acid, 2-cyanoethyl
 ester, monohydrochloride salt (8,9); (6634-40-8)
 Thiourea: Urea, thio- (8); Thiourea (9); (62-56-6)

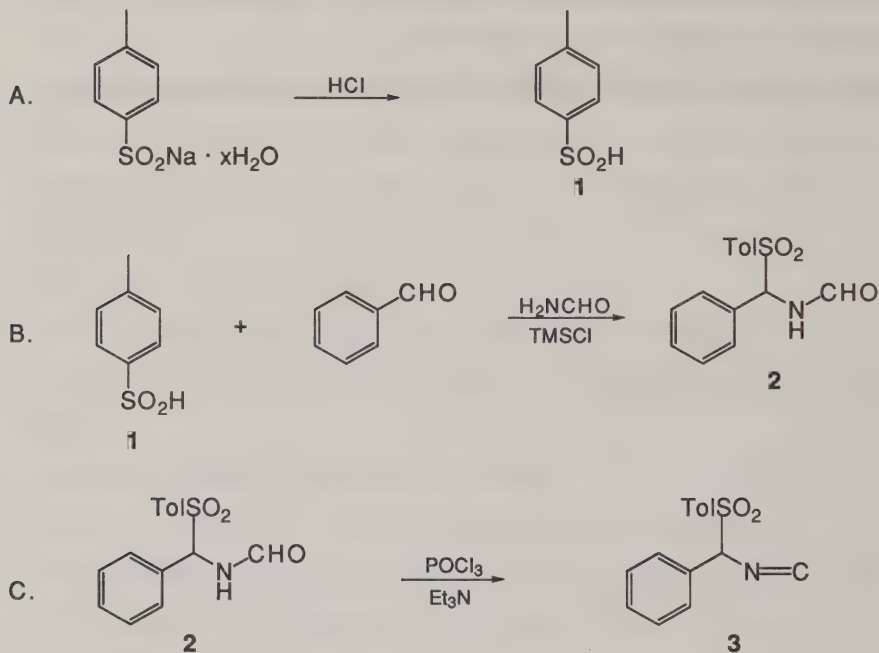
3-Chloropropionitrile: Propionitrile, 3-chloro- (8); Propanenitrile, 3-chloro- (9); (542-76-7)

3-(Trimethylsilyl)propanesulfonic acid, sodium salt: 1-Propanesulfonic acid, 3-(trimethylsilyl)-, sodium salt (8,9); (2039-96-5)

3,3'-Dithiobispropionitrile: Propanenitrile, 3,3'-dithiobis- (9); (42841-31-6)

α -TOSYLBENZYL ISOCYANIDE

(Benzene,1-[(isocyanophenylmethyl)sulfonyl]-4-methyl-)



Submitted by Joseph Sisko,¹ Mark Mellinger,¹ Peter W. Sheldrake,² and Neil H. Baine.¹

Checked by Yan Dong and Steven Wolff.

1. Procedure

A. *p*-Toluenesulfonic acid (1). A 2-L Erlenmeyer flask equipped with a magnetic stir bar is charged with 670 mL of water and 134.1 g (536 mmol) of *p*-toluenesulfonic acid, sodium salt (Note 1) and the mixture is stirred for 20-30 min until a clear solution

is obtained. *tert*-Butyl methyl ether (TBME, 670 mL) is added followed by the slow addition of 44 mL of concentrated aqueous hydrochloric acid (HCl) (536 mmol) over 5 min. The mixture is stirred for an additional 20-30 min, transferred to a separatory funnel and the aqueous layer is removed. The organic layer is diluted with 670 mL of toluene and concentrated with a rotary evaporator (Note 2) until approximately 70-90% of the solvent has been removed. Heptane (200 mL) is added and the white solid is collected by filtration using a Büchner funnel, rinsed with 270 mL of heptane and dried under vacuum for 2-4 hr (Note 2) to give 71-76 g (85-91%) of *p*-toluenesulfonic acid (Note 3) that is used in the next step (Note 4).

B. N-(α -Tosylbenzyl)formamide (2). A 1-L, three-necked, round-bottomed flask fitted with an overhead stirrer, a reflux condenser capped with a nitrogen (N₂) inlet and a temperature probe is charged with 55 mL of acetonitrile and 55 mL of toluene (Note 5), 10.7 mL (105.6 mmol) of benzaldehyde (Note 6), 10.5 mL (264 mmol) of formamide (Note 6) and 14.7 mL (116 mmol) of chlorotrimethylsilane (Note 6). After heating the solution at 50°C for 4-5 hr, 24.7 g (158.3 mmol) of *p*-toluenesulfonic acid (**1**) (Note 7) is added and heating is continued for an additional 4-5 hr. The solution is cooled to room temperature and 55 mL of TBME is added. The solution is stirred for 5 min and 275 mL of water is added. The resulting mixture is cooled to 0°C, held there for 1 hr and the precipitated white solid is collected using a Büchner funnel. The reaction flask is washed with 35 mL of TBME and this rinse is poured over the filter cake. After washing with TBME a second time, the solid is dried in a vacuum oven at 60°C for 5-10 hr to give 26.6-29.1 g (85-94%) of *N*-(α -tosylbenzyl)formamide (**2**) which is used in the next step without further purification (Note 8).

C. α -Tosylbenzyl isocyanide (3) (Note 9). A 1-L, three-necked, round-bottomed flask fitted with an overhead stirrer, a 100-mL addition funnel and a temperature probe is charged with 200 mL of tetrahydrofuran (THF) (Note 10) and 27.6 g (94.8 mmol) of *N*-(α -tosylbenzyl)formamide (**2**). Phosphorus oxychloride (17.7 mL, 190 mmol) (Notes

11, 12) is added and the resulting solution is stirred for 5 min at 25°C. After cooling the solution to 0°C, 79.3 mL (569 mmol) of triethylamine (Notes 11, 12) is added slowly over 30-45 min while keeping the internal reaction temperature below 10°C. After the triethylamine addition is complete, the reaction is warmed to 5-10°C and held there for 30-45 min. Ethyl acetate (140 mL) and water (140 mL) are added sequentially to the reaction, the mixture is stirred for 5 min and, after transferring the mixture to a separatory funnel, the aqueous layer is removed. The organic layer is washed with water (2 x 140 mL), saturated sodium bicarbonate (NaHCO₃) solution (140 mL) and brine (70 mL). The organic layer is transferred to a 500-mL, round-bottomed flask and concentrated on a rotary evaporator (Note 13). The residue is diluted with 140 mL of 1-propanol (Notes 11, 14) and this solution is concentrated on a rotary evaporator to half of its original volume. The residue is cooled to 5-10°C for 30 min and the beige solid that crystallizes is filtered through a Büchner funnel. The filter cake is rinsed twice with 75 mL of 1-propanol. The beige solid is dried under vacuum for 3-4 hr (Note 13) to give 18.1-19.7 g (70-76%) of α -tosylbenzyl isocyanide (**3**) (Note 15).

2. Notes

1. p-Toluenesulfinic acid, sodium salt, purchased from the Aldrich Chemical Company, Inc., was used without purification and was found to be a tetrahydrate.

2. Minor decomposition of p-toluenesulfinic acid is observed at temperatures above 55°C. For this reason, the water bath of the rotary evaporator and all subsequent heating operations should be kept at temperatures below 35-40°C to obtain best results.

3. p-Toluenesulfinic acid should be used immediately after its preparation or stored under N₂ and used within 2-3 weeks.

4. The spectra are as follows: ^1H NMR (300 MHz, DMSO-d_6) δ : 2.36 (s, 3 H), 7.35 (d, 2 H, $J = 8.1$), 7.54 (d, 2 H, $J = 8.1$); ^{13}C NMR (75 MHz, DMSO-d_6) δ : 18.7, 122.9, 127.9, 140.85, 143.6.

5. Reagent grade toluene and acetonitrile supplied by J.T. Baker Inc. were used without further purification.

6. Fresh bottles of benzaldehyde (99%), formamide (99+%) and chlorotrimethylsilane (98%) from the Aldrich Chemical Company, Inc., were used without further purification.

7. The 50 mol % excess of *p*-toluenesulfinic acid is required to obtain the best results. Using only 10-20 mole % excess of the sulfinic acid typically lowers the yield by 20-30%. This has been attributed to the known propensity of arylsulfinic acids to disproportionate.³ The checkers noted the presence of insoluble material after the addition of *p*-toluenesulfinic acid. This did not effect the yield.

8. Compound **2** exists as a 5:1 mixture of amide rotamers at 25°C in DMSO-d_6 . The spectra for the major rotamer are as follows: ^1H NMR (300 MHz) δ : 2.40 (s, 3 H), 6.38 (d, 1 H, $J = 10.6$), 7.42 (m, 5 H), 7.55 (m, 2 H), 7.70 (d, 2 H, $J = 8.1$), 7.96 (s, 1 H), 9.75 (d, 1 H, $J = 10.6$); ^{13}C NMR (75 MHz, DMSO-d_6) δ : 21.0, 70.2, 128.1, 129.0, 129.1, 129.3, 129.45, 130.3, 133.4, 144.7, 160.1; mp 172-173°C (lit.⁴ 160-162°C); IR (KBr) cm^{-1} : 3336, 1654, 1320, 1145. Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_3\text{S}$: C, 62.27; H, 5.23; N, 4.84. Found C, 61.97; H, 5.11; N, 4.71.

9. Step C is a modified literature procedure.⁴

10. A new bottle of reagent grade THF (water content < 0.02%) from J. T. Baker Inc. was used without further purification.

11. Phosphorus oxychloride (99%), triethylamine (99%), and 1-propanol (99+%) were purchased from the Aldrich Chemical Company, Inc., and used without further purification. The checkers noted the presence of insoluble material after addition of the phosphorus oxychloride.

12. The excess amounts of phosphorus oxychloride and triethylamine are required to ensure that the reaction goes to completion. Using lesser amounts of these reagents leads to incomplete reactions.

13. Isocyanides similar to **3** have been found to be thermally unstable at temperatures above 80°C. To secure a margin of safety, avoid heating **3** and similar isocyanides at temperatures above 35-40°C.

14. The checkers noted formation of a suspension upon addition of the 1-propanol.

15. The spectra are as follows: mp 145°C dec (lit.⁴ 128-130°C dec); IR (KBr) cm^{-1} : 2131, 1331, 1158; ^1H NMR (300 MHz, CDCl_3) δ : 2.45 (s, 3 H), 5.61 (s, 1 H), 7.39 (m, 7 H), 7.59 (d, 2 H, $J = 8.2$); ^{13}C NMR (75 MHz, CDCl_3) δ : 21.75, 76.6, 126.7, 128.4, 128.7, 129.8, 130.3, 130.5, 130.7, 146.6, 166.4. Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{NO}_2\text{S}$: C, 66.40; H, 4.83; N, 5.16. Found C, 66.42; H, 4.88; N, 5.13.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

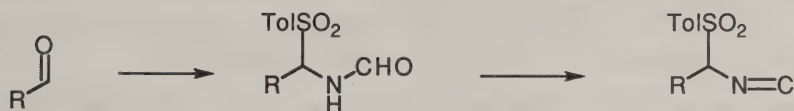
3. Discussion

Tosylmethyl isocyanide (TosMIC) and its congeners are useful and versatile building blocks for the construction of heterocyclic molecules.⁵ While TosMIC is available from a variety of commercial sources, substituted TosMIC reagents have suffered from the lack of general and efficient methods for their preparation.⁶

The present procedure provides ready access to a variety of substituted TosMIC reagents, exemplified by α -tosylbenzyl isocyanide (**3**), by dehydration of the

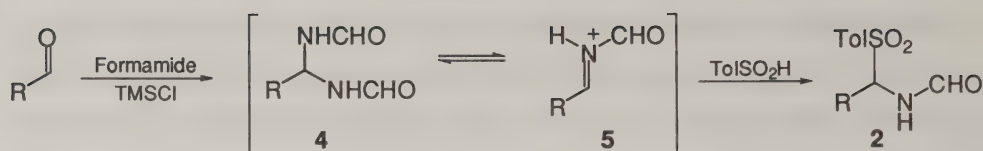
corresponding formamides (**2**). While this route has been employed previously, the reported methods of preparation for formamides **2** suffer from low yields⁷ and extended reaction times.⁴ The present process for preparing these formamides offers high yields, mild conditions and generality, as shown below in the Table.

TABLE
PREPARATION OF SUBSTITUTED TOSMIC REAGENTS



Entry	R	% Yield	% Yield
1	4-F-C ₆ H ₄	93	70-80
2	4-MeO-C ₆ H ₄	92	74
3	3-Thiophene	81	76
4	Me ₂ CHCH ₂	81	58
5	Me ₂ CH	62	60

The reaction proceeds by formation of bisformamide **4**, which can be isolated but is more typically formed and reacted in situ. The bisformamide **4** is presumably in equilibrium with the corresponding iminium ion **5**, which is captured by the sulfinic acid to generate **2**. The TMSCl consumes the water of condensation while liberating HCl, which catalyzes the entire sequence.



1. SmithKline Beecham Pharmaceuticals, Synthetic Chemistry Department, P.O. Box 1539, King of Prussia, PA 19406
2. SmithKline Beecham Pharmaceuticals, Synthetic Chemistry Department Old Powder Mills, Tonbridge TN11 9AN, U.K.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

α -Tosylbenzyl isocyanide: Benzene, 1-[(isocyanophenylmethyl)sulfonyl]-4-methyl- (9); (36635-66-2)

p-Toluenesulfinic acid (8); Benzenesulfinic acid, 4-methyl- (9); (536-57-2)

p-Toluenesulfinic acid, sodium salt (8); Benzenesulfinic acid, 4-methyl-, sodium salt (9); (824-79-3)

tert-Butyl methyl ether: Ether, tert-butyl methyl (8); Propane, 2-methoxy-2-methyl- (9); (1634-04-4)

N-(α -Tosylbenzyl)formamide: Formamide, N-[[(4-methylphenyl)sulfonyl]-phenylmethyl]- (9); (37643-54-2)

Benzaldehyde (8,9); (100-52-7)

Formamide (8,9); (75-12-7)

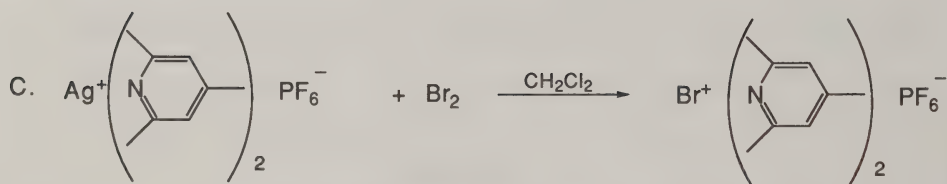
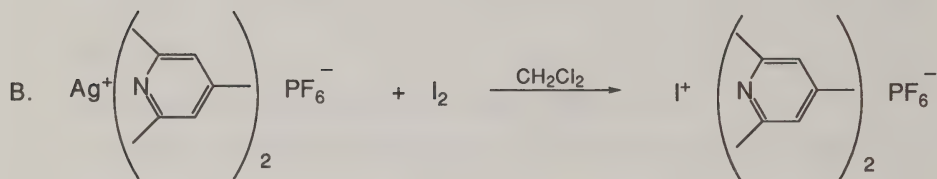
Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

Phosphorus oxychloride: HIGHLY TOXIC: Phosphoryl chloride (8,9); (10025-87-3)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

**PREPARATION OF BIS(2,4,6-TRIMETHYLPYRIDINE)IODINE(I)
HEXAFLUOROPHOSPHATE AND BIS(2,4,6-TRIMETHYLPYRIDINE)
BROMINE(I) HEXAFLUOROPHOSPHATE**

(Iodine(1+), bis(2,4,6-trimethylpyridine)-, hexafluorophosphate(1-), and
Bromine(1+), bis(2,4,6-trimethylpyridine)-, hexafluorophosphate(1-))



Submitted by Fadi Homsí, Sylvie Robin, and Gérard Rousseau.¹

Checked by Suzanne Patterson and David J. Hart.

1. Procedure

Caution! These procedures should be conducted in an efficient fume hood because of the toxicity of iodine and bromine.

A. Bis(2,4,6-trimethylpyridine)silver(I) hexafluorophosphate. A 2-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer and a 250-mL pressure-equalizing dropping funnel. The flask is charged with 1 L of distilled water, 100 g of silver nitrate (0.588 mol) and 109.3 g of potassium hexafluorophosphate (0.594 mol) (Note 1). When all the solids are dissolved, 221 mL of 2,4,6-collidine (1.67 mol) is added over 10 min while stirring (Notes 2, 3). A slight exothermic reaction is observed, corresponding to the formation of a white solid. The mixture is stirred for 1 hr at room temperature, the solid is suction filtered, and the filtercake is washed with 1 L of water. The solid is dried in the dark in a desiccator under high vacuum over phosphorus pentoxide (P_2O_5) for 1 week, to afford 262-291 g (90-99%) of silver salt as a white-gray solid, mp 210°C (Notes 4, 5).

B. Bis(2,4,6-trimethylpyridine)iodine(I) hexafluorophosphate. A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, condenser topped with a drying tube containing calcium chloride, and a stopper is charged with 500 mL of dry methylene chloride (Note 6), 82.5 g of bis(trimethylpyridine)silver(I) hexafluorophosphate (0.166 mol), and 41.9 g of iodine (0.165 mol). The mixture is stirred until all the iodine is consumed (1 hr - 2 hr) (Note 7). The resulting yellow solid (silver iodide) is suction filtered, and washed with 100 mL of dry methylene chloride. The filtrate is concentrated on a rotary evaporator at a maximum bath temperature of 30°C to give 68-76 g (80-88%) of yellowish solid bis(2,4,6-trimethylpyridine)iodine(I) hexafluorophosphate (mp 132-133°C) (Notes 8, 9, and 10). This product is suitable for reactions without further purification.

C. *Bis(2,4,6-trimethylpyridine)bromine(I) hexafluorophosphate*. A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, 50-mL pressure-equalizing addition funnel, and a drying tube containing calcium chloride is charged with 500 mL of dry methylene chloride (Note 6), and 82.5 g of bis(trimethylpyridine)-silver(I) hexafluorophosphate (0.166 mol). Then 8.3 mL of bromine (0.161 mol) is added in 10 min. The mixture is stirred until all the bromine is consumed (1 hr) (Note 11). The resulting yellowish solid (silver bromide) is suction filtered and washed with 100 mL of dried methylene chloride. The filtrate is concentrated on a rotary evaporator at a maximum bath temperature of 30°C to give 65-74 g (83-95%) of bis(2,4,6-trimethylpyridine)bromine(I) hexafluorophosphate (mp 127-128°C) as a white solid (Notes 9, 12, and 13). This product is suitable for reactions without further purification.

2. Notes

1. Silver nitrate was obtained from ACROS and potassium hexafluorophosphate from Aldrich Chemical Company, Inc.

2. Collidine (99% grade) from Aldrich Chemical Company, Inc. was used. Technical grade (from ACROS) can be used after purification by distillation from calcium hydride (CaH_2).

3. The checkers always observed a small amount of undissolved solid and began the addition of collidine when dissolution appeared to cease.

4. The range of melting is 210°-253°C. At 253°C the submitters observe solid decomposition. The checkers observed an mp range of 222-238°C (dec.).

5. The NMR spectrum was as follows: ^1H NMR (250 MHz, CDCl_3) δ : 2.40 (s, 6 H), 2.78 (s, 12 H), 7.11 (s, 4 H). ^{13}C NMR (63 MHz, CD_2Cl_2) δ : 21.6, 28.0, 124.4, 153.9, 158.2. Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{AgF}_6\text{N}_2\text{P}$: C, 38.81; H, 4.48; N, 5.66. Found: C, 38.73; H, 4.36; N, 5.59.

6. Methylene chloride was dried by distillation over CaH_2 .

7. It is important that all the iodine reacts with the silver salt. After concentration, the presence of iodine can catalyze the decomposition of bis(trimethylpyridine)iodine(I) hexafluorophosphate. If necessary a small amount of silver salt can be added.

8. The submitters note that after recrystallization from methylene chloride a white solid is obtained [mp 131-132°C (dec)]. No difference in reactivity is observed compared with the crude product.

9. This solid must be stored in the dark at 0°C. In these conditions it can be kept for several years, or for several months at room temperature.

10. The following spectra were obtained: ^1H NMR (250 MHz, CDCl_3) δ : 2.41 (s, 3 H), 2.43 (s, 3 H), 2.65 (s, 6 H), 2.85 (s, 6 H), 7.11 (s, 2 H), 7.17 (s, 2 H); ^{13}C NMR (63 MHz, CD_2Cl_2) δ : 21.5, 29.9, 125.9, 155.0, 158.3; IR (KBr) cm^{-1} : 2989 (vs), 1618 (s), 1461 (s), 1384 (s), 1312 (s), 1031 (s), 1003 (s), 829 (br). Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{F}_6\text{I}_2\text{N}_2\text{P}$: C, 37.37; H, 4.31; N, 5.45. Found: C, 37.45; H, 4.36; N, 5.42.

11. All the bromine should have reacted before removal of the solvent. See Note 7.

12. The submitters indicate that after recrystallization from methylene chloride the mp is 125°C (decomposition). No difference in reactivity is observed compared with the crude product.

13. The following spectra were obtained: ^1H NMR (250 MHz, CDCl_3) δ : 2.43 (s, 6 H), 2.78 (s, 12 H), 7.16 (s, 4 H); ^{13}C NMR (63 MHz, CD_2Cl_2) δ : 21.6, 25.9, 126.3, 154.9, 156.4; IR (KBr) cm^{-1} : 2990 (vs), 1618, (s), 1463 (s), 1386 (s), 1313 (s), 1030 (s), 1005 (s), 828 (br).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

These preparations of bis(2,4,6-trimethylpyridine)iodine(I) and bromine(I) hexafluorophosphate are adaptations of methods previously reported for obtaining the corresponding perchlorates.²

The advantages of the hexafluorophosphate salts compared to the perchlorate salts are the safety of preparation, ease of use, and their low hygroscopicities. This method of preparation can be applied to a large variety of mono aromatic amines (pyridine, chloropyridine, 2-methoxypyridine, etc.); however, in the reactions that the submitters have examined these salts are less reactive than the parent collidine salts. Bis(2,4,6-trimethylpyridine)iodine(I) and -bromine(I) hexafluorophosphate have been used for specific electrophilic halogenations, such as the preparation of 7-membered ring lactones³ and ethers,⁴ medium ring lactones,^{3,5} halogenation of phenols,⁶ pyridinols⁷ and acetylenic compounds.⁸ Most of these reactions are impossible or difficult with other known halogenation reagents.

1. Laboratoire des Carbocycles (Associé au CNRS), Institut de Chimie Moléculaire d'Orsay, Bât. 420, Université de Paris-Sud, 91405 Orsay, France.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Bis(2,4,6-trimethylpyridine)iodine(I) hexafluorophosphate: Iodine(1+) bis(2,4,6-trimethylpyridine)-, hexafluorophosphate(1-) (12); (113119-46-3)

Bis(2,4,6-trimethylpyridine)bromine(I) hexafluorophosphate: Bromine(1+) bis(2,4,6-trimethylpyridine)-, hexafluorophosphate(1-) (14); (188944-77-6)

Silver(I)nitrate: Nitric acid silver(1+) salt (8,9); (7761-88-8)

Potassium hexafluorophosphate. Phosphate(1-), hexafluoro, potassium (8,9); (17084-13-8)

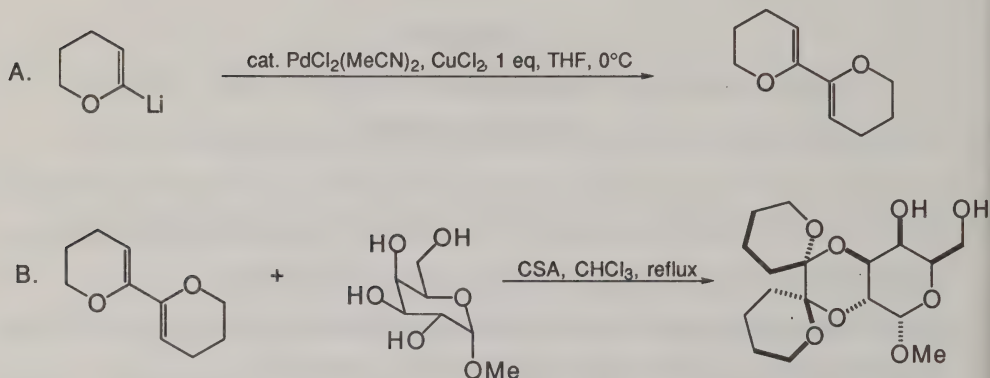
2,4,6-Collidine: Pyridine, 2,4,6-trimethyl- (8,9); (108-75-8)

Iodine (8,9); (7553-56-2)

Bromine (8,9); (7726-95-6)

METHYL 2,3-O-(6,6'-OCTAHYDRO-6,6'-BI-2H-PYRAN-2,2'-DIYL)- α -D-GALACTOPYRANOSIDE

(α -D-Galactopyranoside, methyl, 2,3-O-(octahydro[2,2'-bi-2H-pyran]-2,2'-diyl-, [2(2R,2'R)-])



Submitted by Steven V. Ley^{1a} and Helen M.I. Osborn.^{1b}

Checked by Laurent Ducry, Leïla Abrous, and Amos B. Smith, III.

1. Procedure

A. *6,6'-Bi(3,4-dihydro-2H-pyran) (Bis-DHP)* (Note 1). A 500-mL, two-necked flask (Flask A) equipped with a magnetic stirrer is flushed with dry argon and then charged with 30 mL of dry distilled 3,4-dihydro-2H-pyran (329 mmol) and 60 mL of dry tetrahydrofuran (THF) (Note 2). Stirring is begun and the solution is cooled to -78°C by means of external cooling. An inert argon atmosphere is maintained throughout the reaction. *tert*-Butyllithium in pentanes (200 mL of a 1.7 M solution, 340 mmol) is added dropwise under argon and the resultant cloudy mixture is stirred at 0°C (ice/water bath) for 1 hr. Meanwhile, another 1-L flask (Flask B) equipped with a magnetic stirrer

is flushed with dry argon (an inert argon atmosphere is again maintained throughout the reaction) and then charged with 2.0 g of palladium(II) chloride bis(acetonitrile) complex (2.2 mol%, 7.4 mmol), 46.3 g of copper(II) chloride (344 mmol) and 300 mL of dry THF. Stirring is initiated and the slurry is cooled to 0°C by means of external cooling. When the slurry has reached 0°C, the clear pale yellow solution from Flask A is added via cannula to cooled Flask B at 0°C. The orange brown slurry becomes black and the resultant mixture is stirred at 0°C for 1 hr. An aqueous saturated ammonium chloride / concentrated ammonium hydroxide solution (4:1, pH 10) is added to quench the reaction and the solution is extracted with ether (3 x 200 mL). The combined ether extracts are dried over magnesium sulfate (MgSO₄), filtered and concentrated under reduced pressure to give a yellow solid. This is purified by column chromatography on silica gel (Merck 9385, 6 cm x 20 cm) eluting with 1% triethylamine / 5% ether / 94% petroleum ether to yield 15.0 g of 6,6'-bi(3,4-dihydro-2H-pyran) (Bis-DHP) as a white crystalline solid (55%) (Notes 3 and 4).

B. Methyl 2,3-O-(6,6'-octahydro-6,6'-bi-2H-pyran-2,2'-diyl)- α -D-galactopyranoside. A 100-mL, two-necked flask equipped with a magnetic stirrer, condenser and heating mantle is flushed with dry argon and then charged with 2.8 g of methyl α -D-galactopyranoside (14.4 mmol), 50 mL of dry chloroform and 5.0 g of Bis-DHP (30.1 mmol) (Notes 5 and 6). The solution is maintained under an argon atmosphere and 0.14 g of DL-camphorsulfonic acid (0.6 mmol) is added. The mixture is heated under reflux for 1.5 hr. After this time, 4.6 mL of anhydrous ethylene glycol (83.3 mmol) (Note 7) is added and heating is continued for a further 0.5 hr. The heating mantle is removed and the solution cooled to room temperature. The resultant solution is diluted with 100 mL of dichloromethane, made basic by the addition of potassium carbonate (approximately 0.5 g required), filtered and concentrated under reduced pressure. The crude material is purified by column chromatography on silica gel (Merck 9385, 6 cm x 30 cm) eluting with 80-100% ethyl acetate/petroleum ether to

yield 3.3 g of methyl 2,3-O-(6,6'-octahydro-6,6'-bi-2H-pyran-2,2'-diyl)- α -D-galactopyranoside as an off-white foam (64%) (Note 8).

2. Notes

1. 6,6'-Bi(3,4-dihydro-2H-pyran), 98% (Bis-DHP) is commercially available from Aldrich Chemical Company, Inc., P.O. Box 355, Milwaukee, WI 53201, USA. Catalog # 34,973-9.

2. Because of the sensitivity of the reagents toward moisture, both procedures A and B should be carried out in oven-dried glassware under dry and inert conditions.

3. Pure bis(dihydropyran) is a white and relatively stable crystalline solid. As would be expected for an enol ether, it is sensitive to hydrolysis and is best stored for a long time under an inert atmosphere at -10°C .

4. Physical data for purified material are as follows: mp $49-50^{\circ}\text{C}$ (petroleum ether); ^1H NMR (270 MHz, CDCl_3) δ : 1.78-1.87 (m, 4 H), 2.08-2.14 (m, 4 H), 4.01-4.05 (m, 4 H), 5.16 (t, 2 H, $J = 3.8$); ^{13}C NMR (68 MHz, CDCl_3) δ : 20.2, 22.4, 66.2, 96.8, 147.6; m/z (EI) 166 (M^+), 138, 111, 83, 55. Anal. calcd for $\text{C}_{10}\text{H}_{14}\text{O}_2$: C, 72.26; H, 8.49. Found C, 72.24; H, 8.56.

5. The checkers have found that the chloroform must be distilled prior to use to obtain an optimum yield.

6. Although toluene can be used for these reactions, boiling chloroform is preferred. The use of more polar solvents such as dimethylformamide (DMF) or acetonitrile fail to give any products, presumably because of the competitive decomposition of the bis-(dihydropyran). When the solubility of the starting material in boiling chloroform is poor, reaction yields can be improved by applying ultrasound.

7. By-products from this reaction include protection of the primary hydroxyl group and incorporation of only one Bis-DHP ring. These products are less stable

than the desired product and may be deprotected on reaction with ethylene glycol making purification of the reaction mixture much more efficient.

8. Physical data for dispiroketal (dispoke) protected material are as follows: $[\alpha]_D^{23}$ -19.0 (c 1.05 in CHCl_3); ^1H NMR (270 MHz, CDCl_3) δ : 1.42-1.62 (m, 8 H), 1.65-1.85 (m, 4 H), 2.59 (br s, 1 H), 2.84 (br s, 1 H), 3.42 (s, 3 H), 3.55-3.75 (m, 4 H), 3.80-4.00 (m, 3 H), 4.05-4.15 (m, 2 H), 4.23 (dd, 1 H, $J = 10.3, 3.4$), 4.85 (d, 1 H, $J = 3.4$); m/z (EI) 360 (M^+), 200, 167 ($\text{C}_{10}\text{H}_{15}\text{O}_2^+$), 149, 111, 100. Anal. calcd for $\text{C}_{17}\text{H}_{28}\text{O}_8$: C, 56.65; H, 7.83. Found C, 56.42; H, 8.01.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academic Press; Washington, DC, 1995.

3. Discussion

Until recently, the protection of the trans-hydroxyl groups of sugars has been an inefficient process.² This protection has now been simplified by the introduction of the dispiroketal (dispoke) group^{3,4} and the cyclohexane diacetal (CDA) protecting group.⁵ Regiocontrol, in the form of protection of the diequatorial vicinal diol pairs over axial-equatorial or diaxial systems occurs as a result of the stabilizing influence of multiple anomeric effects. Thus a general method for the protection of the diequatorial vicinal diols in a wide range of monosaccharides has been developed (Table 1). In only a few cases when steric interactions are of a lesser magnitude is some cis-diol protection noticed. O-Methyl, S-ethyl or O-pentenyl groups are tolerated at the C-1 carbon of the sugar with the more lipophilic groups enhancing the yields of dispiroketal protection. This reflects the greater solubility of these derivatives in chloroform.

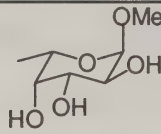
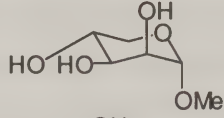
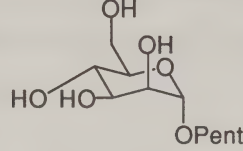
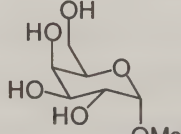
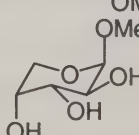
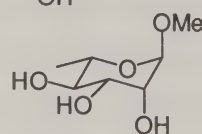
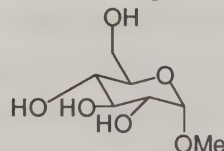
For protection of glucose derivatives, which possess two sets of 1,2-trans diequatorial diols, protection is best achieved by way of **chiral** bis(dihydropyrans).⁶ In this way, complete regioselectivity can be achieved as a result of chirality "matching" of the C-2, C-3 diol pairs with that of the bis(dihydropyran).

The dispiroketal group is stable toward a variety of reaction conditions, including mild acid, and is compatible with glycosidic coupling reactions regardless of whether it is present on the donor or acceptor moiety.⁴ When applied to sugar chemistry, the dispoke moiety can be employed as both a protecting group and a handle for tuning the reactivity of the sugar. This has allowed the concise syntheses of complex oligosaccharides to be achieved.⁷ Finally, the facile cleavage of the dispiroketal unit can be accomplished with 95% trifluoroacetic acid at room temperature.⁴

1. (a) Present addresses: S. V. Ley: University Chemical Laboratories, Lensfield Road, Cambridge, CB2 1EW, UK; (b) H. M. I. Osborn: Department of Chemistry, University of Reading, Whiteknights, Reading, RG6 6AD, UK.
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- 6.** Entwistle, D. A.; Hughes, A. B.; Ley, S. V.; Visentin, G. *Tetrahedron Lett.* **1994**, 35, 777; Edwards, P. J.; Entwistle, D. A.; Genicot, C.; Ley, S. V.; Visentin, G. *Tetrahedron: Asymmetry* **1994**, 5, 2609.
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TABLE I
PROTECTION FOR DIEQUATORIAL VICINAL DIOLS

Sugar	3,4-Protection	2,3-Protection
	0%	76%
	62%	0%
	45%	0%
	0%	64%
	40%	58%
	47%	32%
	26%	42%

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl 2,3-O-(6,6'-octahydro-6,6'-bi-2H-pyran-2,2'-diyl)- α -D-galactopyranoside:
 α -D-Galactopyranoside, methyl, 2,3-O-(octahydro[2,2'-bi-2H-pyran]-
2,2'-diyl-, [2(2R,2'R)]- (13); (144102-32-9)

6,6'-Bi(3,4-dihydro-2H-pyran) [Bis-DHP]: 6,6'-Bi-2H-pyran, 3,3',4,4'-tetrahydro-
(12); (109669-49-0)

3,4-Dihydro-2H-pyran: 2H-Pyran, 3,4-dihydro- (8,9); (110-87-2)

tert-Butyllithium: Lithium, tert-butyl- (8); Lithium, (1,1-dimethylethyl)- (9); (594-19-4)

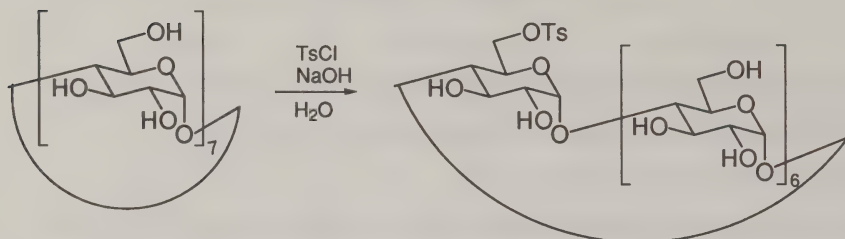
Palladium(II) chloride bisacetonitrile: ALDRICH: Bis(acetonitrile)dichloropalladium(II):
Palladium, bis(acetonitrile)dichloro- (8,9); (14592-56-4)

Copper(II) chloride: Copper chloride (8,9); (7447-39-4)

Methyl α -D-galactopyranoside: α -D-Galactopyranoside, methyl (8,9); (3396-99-4)

(\pm)-Camphorsulfonic acid: Boranesulfonic acid, 2-oxo-, (\pm)- (8); Bicyclo[2.2.1]heptane-
1-methanesulfonic acid, 7,7-dimethyl-2-oxo-, (\pm)- (9); (5872-08-2)

6^A-O-p-TOLUENESULFONYL-β-CYCLODEXTRIN
(β-Cyclodextrin, 6^A-(4-methylbenzenesulfonate))



Submitted by Bernadette Brady, Nuala Lynam, Thomas O'Sullivan, Cormac Ahern, and Raphael Darcy.¹

Checked by Kevin M. Shea and Rick L. Danheiser.

1. Procedure

A 3-L, three-necked, round-bottomed flask equipped with a large magnetic stirring bar and thermometer is charged with β-cyclodextrin hydrate (50 g, 44 mmol) (Note 1) and a solution of 25 g of sodium hydroxide in 1.5 L of water. The solution is stirred at 0-5°C in an ice-water bath while p-toluenesulfonyl chloride (20 g, 105 mmol) (Note 2) is added in one portion. The reaction mixture is stirred vigorously for 2 hr at 0-5°C (Note 3), and then another portion of p-toluenesulfonyl chloride (30 g, 157 mmol) (Note 4) is added and the reaction mixture is stirred at this temperature for 3 hr further. The reaction mixture is filtered through Celite in a fritted glass funnel to separate unreacted tosyl chloride (Note 5). The filtrate is cooled at 0-5°C while 10% aqueous hydrochloric acid (HCl, 350 mL) is added. The resulting solution is stored overnight in a refrigerator at 0°C, and then filtered. The product is dried to constant weight over Drierite in a vacuum desiccator to yield 27-28 g of a white solid. This material is

recrystallized (three times) by dissolving it in 175-200 mL of water at the boiling point and then cooling to room temperature (Note 6). Storage in a refrigerator overnight provides 14.0 g (25%) of 6^A-O-p-toluenesulfonyl- β -cyclodextrin as a white solid, mp 163-168°C (dec.) (Note 7).

2. Notes

1. β -Cyclodextrin hydrate was purchased from Aldrich Chemical Company, Inc. and used without further purification.

2. p-Toluenesulfonyl chloride (99%) was purchased from Aldrich Chemical Company, Inc., and used without further purification.

3. The progress of the reaction can be monitored by TLC by working up a sample of the reaction mixture: filter through Celite, cool to 0°C, and acidify to pH 1 with 10% aqueous HCl. The solid that precipitates is isolated by filtration and dissolved in dimethylformamide (DMF) for TLC analysis on Merck precoated-silica gel 60 plates with methyl ethyl ketone-methanol-water (4:1:1) as eluent, developed by dipping in 5% sulfuric acid-ethanol and heated to 450°C (e.g., with a Bunsen burner). R_F values are 0.25 for β -cyclodextrin, 0.5 for monotosylate and 0.65 for a second product, probably ditosylate.

4. Monitoring by TLC indicates that the second addition of reagent is necessary to complete the reaction within a reasonable time. Most of the tosyl chloride does not dissolve.

5. Unreacted reagent may be washed with water and reused.

6. Dissolving and cooling to 60°C should be rapid, since significant hydrolysis can occur above this temperature (J. Defaye, personal communication to submitters).

7. Lit.⁵ mp 160-162° (dec.). TLC shows a weak spot for ditosylate, and ¹H NMR integration (aromatic region) shows this impurity to be 8-9%. The physical

properties are as follows: ^1H NMR (500 MHz, DMSO-d_6) δ : 2.42 (s, 3 H), 3.20-3.67 (m, 40 H), 4.16-4.20 (m, 1 H), 4.32 (d, 1 H, $J = 9$), 4.37-4.39 (m, 1 H), 4.45-4.48 (m, 2 H), 4.52-4.53 (m, 3 H), 4.77 (d, 2 H, $J = 3.4$), 4.83-4.84 (m, 5 H), 5.64-5.85 (m, 14 H), 7.42 (d, 2 H, $J = 8.2$), and 7.75 (d, 2 H, $J = 8.2$); ^{13}C NMR (125 MHz, DMSO-d_6) δ : 21.3, 59.3, 59.6, 60.0, 69.0, 69.8, 71.9, 72.1, 72.2, 72.4, 72.5, 72.8, 73.0, 73.1, 80.8, 81.2, 81.4, 81.5, 81.7, 101.3, 101.9, 102.0, 102.3, 127.6, 129.9, 132.7, 144.9; $[\alpha]_{\text{D}}^{20} +131^\circ$ (dimethyl sulfoxide, c 4).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Cyclodextrin monotosylate is the most important derivative of this host molecule for access to modifications on the primary hydroxyl side of the macrocycle.² While there is preferential tosylation of the primary sugar hydroxyl groups,³ the problem of selective derivatization of one of the seven glucose units remains, and this requires that the reaction be monitored to avoid over tosylation. Apart from lack of details for this procedure, previous methods have used pyridine instead of water as solvent; have required dry conditions, which if rigorous, cause formation of a cyclodextrin-pyridine gel;⁴ and have not avoided the risk of chlorination during work-up.⁵ The method described here uses water as solvent; the lower yield is offset by simplicity and by recovery of excess reagent and larger scale. The method is adapted from a procedure that was originally thought to give 2-monotosylate;⁶ this was later corrected.⁷

1. Laboratory for Carbohydrate and Molecular Recognition Chemistry, Department of Chemistry, National University of Ireland, University College, Dublin 4, Ireland.
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4. de Rango, C.; Charpin, P.; Navaza, J.; Keller, N.; Nicolis, I.; Villain, F.; Coleman, A. W. *J. Am. Chem. Soc.* **1992**, 114, 5475.
5. Defaye, J.; Gadelle, A.; Guiller, A.; Darcy, R.; O'Sullivan, T. *Carbohydr. Res.* **1989**, 192, 251. This procedure (not checked) for reaction in pyridine avoids gelling by slow addition (with dissolving) of the cyclodextrin to a large volume of vigorously-stirred pyridine. On a scale of 10 g cyclodextrin (in 100-300 mL pyridine) this procedure can produce a yield of 5 g (40%) monotosylate with the following modifications. After gradual addition of tosyl chloride (1.5 g) in pyridine (15 mL) at 0°C, the stirred solution is kept for 2 hr at 0°C, then 20 hr at room temperature. The same amount of tosyl chloride is then added and the reaction monitored by TLC (direct sampling) every 30 min until all the cyclodextrin has reacted. The reaction is then quenched (to avoid chlorination during work-up) by addition of water. Concentration at 50°C under vacuum to 20 mL is followed by precipitation of product with added excess acetone. This concentration-precipitation cycle is repeated twice, and the combined precipitates are recrystallized from water, at $\leq 60^{\circ}\text{C}$.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

6^A-O-p-Toluenesulfonyl- β -cyclodextrin: β -Cyclodextrin,

6^A-(4-methylbenzenesulfonate) (10); (67217-55-4)

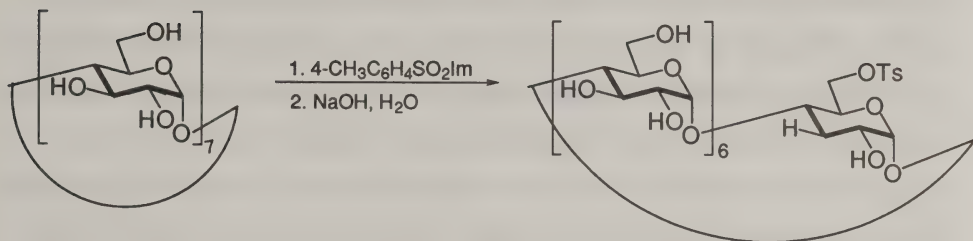
β -Cyclodextrin hydrate: β -Cyclodextrin, hydrate (10); (68168-23-0)

p-Toluenesulfonyl chloride (8); Benzenesulfonyl chloride, 4-methyl- (9): (98-59-9)

N,N-Dimethylformamide: CANCER SUSPECT AGENT: Formamide, N,N-dimethyl-
(8,9); (68-12-2)

6A-O-p-TOLUENESULFONYL- β -CYCLODEXTRIN

(β -Cyclodextrin, 6A-(4-methylbenzenesulfonate))



Submitted by Hoe-Sup Byun, Ning Zhong, and Robert Bittman.¹

Checked by Kevin M. Shea and Rick L. Danheiser.

1. Procedure

1-(p-Toluenesulfonyl)imidazole. A 1-L, three-necked, round-bottomed flask equipped with a thermometer, argon inlet adapter, pressure-equalizing addition funnel, and a magnetic stirbar is charged with a solution of imidazole (65 g, 0.95 mol) (Note 1) in 250 mL of dry dichloromethane (Note 2) and then cooled to 0°C. A solution of p-toluenesulfonyl chloride (80 g, 0.42 mol) in 250 mL of dichloromethane is added dropwise over 1.5 hr. The resulting mixture is allowed to warm to room temperature and then stirred vigorously for 2 hr. The reaction mixture is filtered through a pad of silica gel (100 g), which is washed with 500 mL of 1:1 ethyl acetate-hexane. The filtrate is concentrated under reduced pressure, leaving a residue to which is added 50 mL of ethyl acetate and then 500 mL of hexane. Filtration of the resulting suspension gives 83-84 g (89-90%) of 1-(p-toluenesulfonyl)imidazole as a white solid, mp 78.0-79.0°C (lit.² 77.0-78.5°C; lit.² 78-78.5°C) (Note 3).

6A-O-Toluenesulfonyl-β-cyclodextrin. In a 2-L, three-necked, round-bottomed flask equipped with a thermometer, pressure-equalized dropping funnel, and a large magnetic stirbar, 40.0 g (35.2 mmol) of β-cyclodextrin hydrate (Note 4) is dissolved in 900 mL of water by heating to 60°C with vigorous stirring (Note 5). Stirring is continued as the solution is allowed to cool to room temperature (Note 6), and to the resulting milky suspension is added 31.3 g (141 mmol) of finely powdered 1-(p-toluenesulfonyl)imidazole in one portion (Note 7). After 2 hr, a solution of 18 g (0.45 mol) of sodium hydroxide in 50 mL of water is added over 20 min (Note 8). After 10 min, unreacted 1-(p-toluenesulfonyl)imidazole is separated by filtration through a sintered glass funnel (Note 9). The reaction is quenched by the addition of 48.2 g (0.90 mol) of ammonium chloride (NH₄Cl) with swirling to dissolve all the solids. The resulting mixture is concentrated to about half of its original volume by blowing a stream of air over its surface overnight (Note 10). The product begins to precipitate almost immediately as the mixture becomes more concentrated. The resulting suspension is filtered through a large sintered-glass funnel (ca. 2 hr), and the collected solid is washed with two 100-mL portions of ice water and one 200-mL portion of acetone and then dried to constant weight over calcium chloride in a vacuum desiccator to yield 18 g (40%) (Note 11) of the title compound as a white solid (Note 12).

2. Notes

1. p-Toluenesulfonyl chloride and imidazole were purchased from Aldrich Chemical Company, Inc., and used as supplied.
2. Dichloromethane was stored over calcium hydride and distilled from calcium hydride immediately prior to use.

3. The physical properties are as follows: TLC (silica gel 60 F254 aluminum-backed plates) $R_f = 0.48$ (hexane/EtOAc 1:1); ^1H NMR (400 MHz, CDCl_3) δ : 2.43 (s, 3 H), 7.08 (s, 1 H), 7.30 (s, 1 H), 7.35 (d, 2 H, $J = 8.3$), 7.83 (d, 2 H, $J = 8.3$), 8.02 (s, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ : 21.7, 117.4, 127.1, 130.3, 131.3, 134.7, 136.5, 146.2; GCMS (M^+ electron impact) m/e Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$ 222.05, found 222.05.

4. β -Cyclodextrin hydrate was purchased from Acros Organics, Fisher Scientific Company, and was used without further purification or drying ($R_f = 0.41$, 2-PrOH/ H_2O /EtOAc/concd NH_4OH 5:3:1:1). β -Cyclodextrin and the title compound were dissolved in water, spotted on silica gel 60 F254 aluminum-backed plates (EM Separations Technology), and dried on a hot plate prior to development in the solvent systems indicated.

5. The submitters swirled the mixture on a steam bath to effect dissolution of the cyclodextrin. A clear solution is obtained; otherwise, any undissolved materials, which may promote crystallization of cyclodextrin, should be removed by filtration of the hot solution through a sintered glass funnel.

6. In an alternative procedure (which resulted in approximately the same yield of the title compound), instead of cooling the solution to room temperature, the submitters adjusted the temperature to 45°C , and then added powdered 1-(*p*-toluenesulfonyl)imidazole with vigorous stirring.

7. Because of the heterogeneous nature of this reaction, 1-(*p*-toluenesulfonyl)imidazole was ground using a mortar and pestle before being added to the reaction mixture. Use of large particles of tosylimidazole resulted in lower yields.

8. The solution of sodium hydroxide should be cooled completely to room temperature before it is added. The yield is lower when the sodium hydroxide solution is added at temperatures below or above room temperature.

9. The solution must not be stirred for more than ca. 20 min after addition of the sodium hydroxide solution; otherwise some unreacted 1-(*p*-toluenesulfonyl)imidazole

will undergo hydrolysis. In addition, on prolonged stirring some product does not crystallize, but instead forms an emulsion, and thus the product remains in the mother liquor. The submitters noted that the addition of a large volume of acetone to the mother liquor precipitates some of the product, which may be collected and recrystallized in water.

10. Difficulties were encountered when the solution was concentrated under reduced pressure using a rotary evaporator because of extensive formation of bubbles. Also, some product decomposed at elevated temperature. All the NH_4Cl must be dissolved before air-blowing. Overnight air-blowing is recommended; at longer times, hydrolysis of the product takes place.

11. The submitters obtained the title compound in 51-61% yield (23-28 g).

12. Characterization data for the title compound follows. The submitters report TLC $R_f = 0.59$ (2-PrOH/ H_2O /EtOAc/concd NH_4OH 5:3:1:1) and $R_f = 0.23$ ($\text{CHCl}_3/\text{MeOH}/\text{H}_2\text{O}$ 65:35:8); the checkers observed R_f values of 0.40 and 0.12, respectively, in these solvent systems and visualized the spots by dipping in 5% sulfuric acid-ethanol and heating to 450°C (e.g., with a Bunsen burner). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 2.49 (s, 3 H), 3.20-3.65 (overlap with HDO, m, 40 H), 4.15-4.20 (m, 1 H), 4.30-4.38 (m, 2 H), 4.44-4.57 (m, 2 H), 4.51 (br s, 3 H), 4.76 (br s, 2 H), 4.83 (br s, 4 H), 5.62-5.83 (m, 14 H), 7.42 (d, 2 H, $J = 8.1$), 7.73 (d, 2 H, $J = 8.1$); ^{13}C (100 MHz, $\text{DMSO}-d_6$) δ : 21.2, 59.3-59.9 (m), 68.9, 69.7, 72.0-73.1 (m), 80.8-81.5 (m), 101.3-102.3 (m), 127.6, 129.9, 132.7, 144.8. The submitters observed $[\alpha]_D^{25} +141^\circ$ to 146° (DMSO, c 0.28 to 0.35) and the checkers found $[\alpha]_D^{20} +131^\circ$ (DMSO, c 4); [lit.³ $[\alpha]_D^{20} +131^\circ$ (DMSO, c 4)]. The submitters report the following HPLC data for the product: HPLC Alltech Econosphere amino column (5 mm, 4.6 x 250 mm); $t_R = 4.4$ min (mobile phase: 50% MeOH, 40% MeCN, 10% H_2O); Sedex 55 evaporative light scattering detection. Under these conditions, the t_R of β -cyclodextrin is 5.1 min.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

6^A-O-Toluenesulfonyl- β -cyclodextrin is used frequently to prepare functionalized β -cyclodextrins on a preparative scale. Examples of the wide variety of functional groups that have been introduced include 6-deoxyazido, amino, alkylamino, hydroxyamino, thio, thioalkyl, halo, and formyl.⁴ Selective monotosylation of β -cyclodextrin without formation of a considerable amount of a mixture containing primary and secondary side multi-tosylated by-products has been difficult to achieve.^{3,4} Monotosylation on the primary side has been accomplished in 61% yield by treatment of β -cyclodextrin in water with p-toluenesulfonic anhydride (1.5 equiv), followed by addition of aqueous sodium hydroxide solution to the inclusion complex.⁵ However, difficulty in preparing tosic acid-free p-toluenesulfonic anhydride frequently results in a lower yield of the title compound. To overcome this problem, 1-(p-toluenesulfonyl)imidazole is used here to synthesize the title compound. The use of the imidazolide of tosic acid as the sulfonating reagent rather than p-toluenesulfonyl chloride (TsCl) or p-toluenesulfonic anhydride (Ts₂O) has the following advantages: (1) the aqueous solubility of 1-(p-toluenesulfonyl)imidazole is higher than that of Ts₂O or TsCl; (2) tosylimidazole is more resistant to hydrolysis at room temperature² than are Ts₂O or TsCl, so less free tosic acid would be formed during the sulfonation reaction; and (3) significant multi-tosylation of β -cyclodextrin is not observed, even though 4 equiv of 1-(p-toluenesulfonyl)imidazole are used.

1. Department of Chemistry & Biochemistry, Queens College of The City University of New York, Flushing NY 11367-1597.
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5. Zhong, N.; Byun, H.-S.; Bittman, R. *Tetrahedron Lett.* **1998**, *39*, 2919.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

6^A-O-Toluenesulfonyl- β -cyclodextrin: β -Cyclodextrin, 6^A-(4-methylbenzenesulfonate) (10); (67217-55-4)

1-(p-Toluenesulfonyl)imidazole: Imidazole, 1-(p-tolylsulfonyl)- (8); 1H-Imidazole, 1-[(4-methylphenyl)sulfonyl] (9); (2232-08-8)

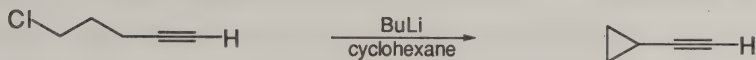
Imidazole (8); 1H-Imidazole (9); (288-32-4)

p-Toluenesulfonyl chloride (8); Benzenesulfonyl chloride, 4-methyl- (9); (98-59-9)

β -Cyclodextrin hydrate: β -Cyclodextrin, hydrate (10); (68168-23-0)

CYCLOPROPYLACETYLENE

(Cyclopropane, ethynyl-)



Submitted by Edward G. Corley, Andrew S. Thompson, and Martha Huntington.¹

Checked by Paul J. Hergenrother and Stephen F. Martin.

1. Procedure

Caution! Butane gas is evolved during the course of the reaction. This preparation should be conducted in a well-ventilated hood.

A 3-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a 1-L pressure-equalizing addition funnel, and a reflux condenser that is topped with a nitrogen inlet. The flask is charged with 102 g (1.0 mol) of 5-chloro-1-pentyne and 250 mL of cyclohexane (Note 1), and the mixture is cooled to 0°C. The cooled solution is reacted with 1.05 L of butyllithium (2.0 M in cyclohexane, 2.1 mol, 2.1 equiv) (Note 2) that is added dropwise via the addition funnel over 1.5 hr maintaining the temperature < 20°C (Note 3). After the addition is complete, the mixture is heated to reflux (78°C) and maintained at reflux for 3 hr (Notes 4, 5). The reaction is cooled to 0° to -10°C and then quenched carefully by the *dropwise* addition of aqueous saturated ammonium chloride (750 mL) (*Caution:* the quench is very exothermic; Note 6.) After the quench is complete, the lower (aqueous) layer is separated and the organic layer is fractionally distilled through a 40-cm x 2.3-cm Hempel column containing Pro-Pak® Monel distillation packing, 0.24" x 0.24" (from Ace Glass). A total of 80-110 mL in the boiling range of 35-78°C is collected. This fraction typically contains 60-80 wt% of cyclopropylacetylene with the remainder being cyclohexane and butane (Notes 7, 8).

The fraction is then distilled a second time through a 30-cm x 2.3-cm packed column and 39-41 g of cyclopropylacetylene, bp 52°-55°C, is collected (58% yield, corrected for purity) (Notes 9, 10).

2. Notes

1. 5-Chloro-1-pentyne was purchased from Farchan Laboratories. It is also available from Aldrich Chemical Company, Inc. A freshly opened bottle of cyclohexane contained 16 µg/mL of water (Karl Fisher). If needed, the cyclohexane can be dried over 3Å or 4Å molecular sieves.

2. The use of butyllithium in cyclohexane rather than hexanes was essential to facilitate product purification. Separation of cyclopropylacetylene (bp 52°C) from hexanes (bp 69°C) was more difficult than from cyclohexane (bp 81°C).

3. A thick precipitate was formed as the butyllithium was added. Care should be taken to avoid excessive splashing of the solid onto the walls of the flask, which can result in decreased yield.

4. The reaction was kept under a slight positive pressure of nitrogen that was vented through an oil bubbler. The butane gas escapes through the bubbler during the reflux. An efficient condenser cooled with water from an ice/water bath is necessary.

5. The reaction was monitored by GLC using an HP-5 column: 25-m x 0.32-mm x 0.52-mm fused silica capillary column with a flow rate of 0.5 mL/min of helium.

6. The temperature of the reaction mixture in this highly exothermic manipulation should be kept below 20°C to avoid loss of the low-boiling product. An addition funnel can be used for the dropwise delivery of the aqueous saturated ammonium chloride solution, while leaving the reflux condenser in place.

7. The receiving flask should be cooled in an ice bath to minimize loss of product.

8. If the distillation was terminated sooner, e.g. at 60°C, a significant amount of cyclopropylacetylene was left in the pot. The pot residue should be assayed to ensure that a significant amount of product was not left behind.

9. This fraction typically contains 5-7 mol% of cyclohexane as measured by NMR. Collection of a narrower boiling range can yield product with less cyclohexane but at lower recovery.

10. The product showed the following NMR data: ^1H (300 MHz, CDCl_3) δ : 0.65-0.78 (m, 4 H), 1.17-1.27 (m, 1 H), 1.73 (d, 1 H, $J = 2.2$). The sample also exhibited a singlet at δ 1.4 corresponding to 7.6 mol% of cyclohexane; ^{13}C (75 MHz, CDCl_3) δ : -0.8, 8.1, 63.4, 87.6 and cyclohexane at 26.9.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Cyclopropylacetylene has been prepared in a two-step procedure by dichlorination of cyclopropyl methyl ketone with phosphorus pentachloride (PCl_5) followed by double dehydrohalogenation with strong base.²⁻⁷ This sequence presented significant scale-up problems and the overall yields were low (20-25%). Results in our hands have been unreliable, especially for the chlorination step that employs solid PCl_5 followed by quenching over ice. The reaction must be kept cold to prevent opening of the cyclopropyl ring by hydrogen chloride (HCl) to give 2,5-dichloro-2-pentene, which was a major by-product and often the only product of the reaction. Hanack and Bässler⁵ report quantitative cyclopropane ring opening unless

highly purified PCl_5 was employed. Hanack⁶ was able to improve the chlorination step by using carbon tetrachloride (CCl_4) as the reaction solvent, but his overall yield to cyclopropylacetylene was only 21%. Salaun⁷ improved the elimination step by use of potassium t-butoxide in dimethyl sulfoxide (DMSO). In a similar manner cyclopropylacetylene has been prepared by base-induced dehydrohalogenation of bromovinylcyclopropane.² Cyclopropylacetylene has also been prepared from the 1-trimethylsilyl derivative of cyclopropylacetylene, which was prepared by treatment of 5-chloro-1-trimethylsilyl-1-pentyne with lithium diisopropylamide at -78°C followed by warming to room temperature, although no details for the desilylation reaction and product isolation are given.⁸

The method presented here offers the advantage of being a one-pot procedure from a commercially available starting material. The initially formed acetylide anion of 5-chloro-1-pentyne undergoes a second deprotonation to the dianion that then cyclizes to cyclopropylacetylide anion. Cyclopropylacetylene itself is a useful building block, but this method can be extended as an in situ source of cyclopropylacetylide anion that can be trapped with a variety of electrophiles to give other useful building blocks. For example, we have used this method to synthesize trifluoromethyl cyclopropylethynyl ketone in 60% isolated yield by quenching the acetylide anion with ethyl trifluoroacetate.

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Appendix

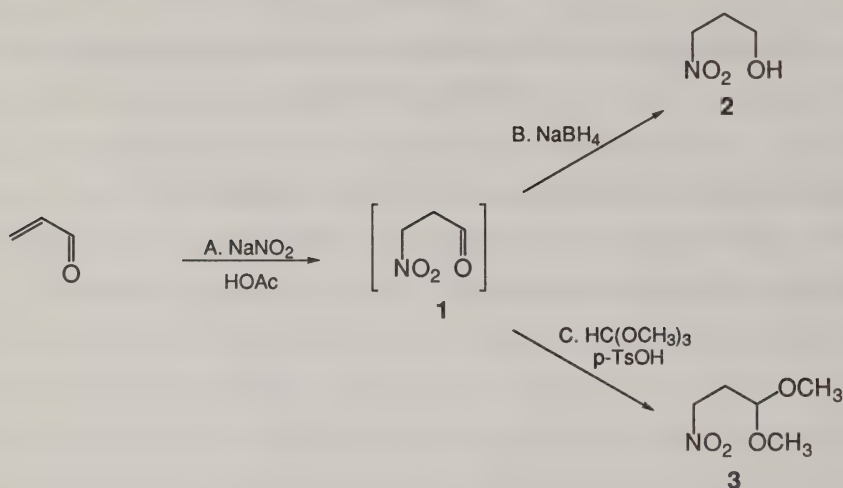
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Cyclopropylacetylene: Cyclopropane, ethynyl- (8,9); (6746-94-7)

5-Chloro-1-pentyne: 1-Pentyne, 5-chloro- (8,9); (14267-92-6)

Butyllithium: Lithium, butyl- (8); (109-72-8)

**3-NITROPROPANAL, 3-NITROPROPANOL,
AND 3-NITROPROPANAL DIMETHYL ACETAL**
(Propanal, 3-nitro-; 1-Propanol, 3-nitro-; and
Propane, 1,1-dimethoxy-3-nitro-)



Submitted by H. Griesser, R. Öhrlein, W. Schwab, R. Ehrler, and V. Jäger.¹

Checked by James P. Davidson and Stephen F. Martin.

1. Procedure

Caution! Distillation of nitroalkanes in general should be conducted behind a safety shield. To avoid decomposition of distillation residues the distillation apparatus should be cooled to 0°C prior to ventilating with inert gas.

A. 3-Nitropropanal (1). A 1-L, round-bottomed flask equipped with a magnetic stirring bar, a 50-mL pressure-equalizing dropping funnel, and a Schlenk-type adapter to keep the reaction mixture under nitrogen (Note 1), is charged with 43.5 g (0.630

mol) of sodium nitrite (Note 2), 125 mL of water (Note 3), and 200 mL of tetrahydrofuran (Note 4). To the well-stirred solution at 0°C is added 33.4 mL (28.0 g, 0.500 mol) of acrolein (Note 5), then 31.5 mL (33.0 g, 0.550 mol) of acetic acid is added over a period of 30-45 min (Note 6). The reaction mixture is stirred at 0°C for another 3 hr. Then 250 mL of ethyl acetate (Note 7) and 100 mL of aqueous saturated sodium bicarbonate are added and the reaction mixture is transferred to a 1-L separatory funnel for complete neutralization, by thorough, but cautious shaking (CO₂ gas develops). The aqueous phase is separated and extracted with ethyl acetate (3 x 50 mL, Note 7). The organic layers are combined and washed with brine (3 x 20 mL), dried (MgSO₄, with stirring for 2 hr), filtered, and concentrated by rotary evaporation (20 mbar, 15 mm, 30°C). The yellow oil obtained is submitted to azeotropic distillation with toluene (2 x 50 mL, 20 mbar, 15 mm, 30°C) to remove residual water and acetic acid to give 46.0-47.0 g (89-91%) of **1** (Notes 8, 9). This material is used without further purification in parts **B** and **C**.

B. 3-Nitropropanol (2). A 1-L, round-bottomed flask, equipped with a magnetic stirring bar and a Schlenk-type adapter (Note 1), is charged with 47.0 g (0.456 mol) of crude 3-nitropropanal and 450 mL of methanol (Note 10). To the stirred solution at -20°C (Note 11) is added 17.26 g (0.456 mol) of sodium borohydride (Note 12) in 10 portions over a period of 30 min; stirring at this temperature is continued for 1 hr. Methyl orange (0.1 mL of 0.1% solution in water) is added to the solution, followed by about 50 mL of 7.5 N hydrochloric acid in methanol (Note 13) until the suspension turns pink (Note 14). After stirring is continued at -20°C for another 30 min, the mixture is allowed to warm to room temperature over a period of 15 min and then concentrated by rotary evaporation (30°C, 20 mbar, 15 mm). The pink residue is treated with 85 g of ice and 450 mL of ethyl acetate (Note 7), then transferred to a 1-L separatory funnel. The organic layer is separated and washed with a mixture of 1 N aqueous potassium bicarbonate and brine (2 x 20 mL, 1:3). The aqueous layers are combined and

extracted with ethyl acetate (2 x 100 mL, Note 7) as described above. The combined organic solutes are thoroughly dried (MgSO_4 , stirring for 2 hr), filtered, and concentrated by rotary evaporation (20 mbar, 15 mm, 30°C). The residual yellow oil is purified by distillation (Note 8) in a Kugelrohr apparatus (air bath temperature: 70°C, 0.034 mbar, 0.02 mm; the product is collected by cooling with ice; duration of the distillation: ca. 90 min) to yield 34.3-34.8 g (73-74%; 65-66%, overall) of pure 3-nitropropanol as a pale yellow oil (Note 15).

C. 3-Nitropropanal dimethyl acetal (3). A 1-L, round-bottomed flask, equipped with a magnetic stirring bar and a Schlenk-type adapter (Note 1), is charged with 47.0 g (0.456 mol) of crude 3-nitropropanal, 150 mL of methanol (Note 10) and 63.7 g (0.600 mol) of trimethyl orthoformate (Note 16). The stirred solution is cooled to 0°C, then 1.8 g of p-toluenesulfonic acid monohydrate (Note 17) is added and the mixture is stirred at room temperature for 4 hr (Note 18). After the volatile material is removed on a rotary evaporator (20 mbar, 15 mm, 30°C), the remaining dark liquid is neutralized with 30 mL of aqueous saturated sodium bicarbonate and diluted with 50 mL of ethyl acetate (Note 7). The mixture is transferred to a 500-mL separatory funnel, and the aqueous layer is separated and extracted with ethyl acetate (3 x 50 mL). The combined organic layers are washed with brine (2 x 20 mL), treated with MgSO_4 and 0.5 g of charcoal (Note 19), filtered, and concentrated by rotary evaporation (20 mbar, 15 mm, 30°C). The residual dark-yellow oil is purified by distillation (Note 8) in a Kugelrohr apparatus (air bath temperature: 55°C, 0.4 mbar, 0.3 mm); the product is collected by cooling with ice; duration of the distillation: ca. 90 min) to afford 46.2-48.2 g (68-71%; 63-65% overall) of pure 3-nitropropanal dimethyl acetal as a pale yellow oil (Notes 20, 21).

2. Notes

1. The reaction mixture is kept under nitrogen passed through a Sicapent® (E. Merck) drying tube.
2. Sodium nitrite (NaNO_2) p.a. was obtained in 1-kg samples from Merck-Schuchardt, Hohenbrunn, Germany.
3. Smaller amounts of water decrease the yield of 3-nitropropanal. If absolute solvents and reagents are used, only 10% of the nitroaldehyde is obtained.
4. Tetrahydrofuran (THF) p.a. was purchased from Merck-Schuchardt, Hohenbrunn, Germany.
5. Acrolein p.a. from Merck-Schuchardt, Hohenbrunn, Germany was distilled prior to use through a 20-cm, silver-plated, Vigreux column with a 4-cm outer and 1.5-cm inner diameter (bp 52°C).
6. The reaction is carried out in the dark to avoid decomposition and side reactions. Acetic acid p.a. was obtained from Merck-Schuchardt, Hohenbrunn, Germany.
7. Ethyl acetate (technical grade) was purified by distillation. The checkers found that reagent grade ethyl acetate could be used without purification.
8. **Caution!** See introductory warning. The submitters report that **1** can be distilled in a Kugelrohr apparatus using a manifold with high-vacuum stopcocks (air bath temperature: 55°C , 0.001 mbar, 0.0007 mm); the product is collected by cooling with ice; duration of the distillation: ca. 90 min; ventilation with nitrogen should occur after ice-cooling of the distillation flask) to afford analytically pure, almost colorless **1** in 75% yield (GLC analysis: $R_t = 7.1$ min, content of **1** >99%, see Note 9 for conditions).
Explosion hazard! Do not attempt to distill **1** unless 0.001 mbar (0.0007 mm) vacuum is available; the temperature of the bath should not exceed 60°C . The checkers found that distillation of the product at 0.04 mbar (0.03 mm), 70°C gave 35-

40% yield of **1** as a yellow oil, and that the distillation residues, even when cooled and ventilated with an inert atmosphere, were prone to violent decomposition.

9. GLC analysis is as follows: $R_t = 7.1$ min, content of **1** >95% [column PS 086/32 mm x 20 m glass capillary, 86:14 dimethyl/phenyl silicone; on-column injection; program: $T_1 = 40^\circ\text{C}$ (1 min), rate $5^\circ\text{C}/\text{min}$, $T_2 = 300^\circ\text{C}$; carrier gas: 0.4 bar (300 mm) H_2]. The content of **1** is >90% according to ^1H and ^{13}C NMR. The product thus obtained decomposes on storage and should be used for further transformations within a few days. The spectroscopic data of 3-nitropropanal are as follows: ^{13}C NMR (125 MHz, CDCl_3) δ : 39.5, 67.7, 197.2; ^1H NMR (500 MHz, CDCl_3) δ : 3.19 (t, 2 H, $J = 6.0$), 4.69 (t, 2 H, $J = 6.0$), 9.79 (s, 1 H); IR (CHCl_3) cm^{-1} : 2844, 1723, 1561, 1375; mass spectrum (CI) m/z 104.0350 [$\text{C}_3\text{H}_6\text{NO}_3$ ($M+1$) requires 104.0348] 104 (base), 86.

10. Methanol p.a. was obtained from Merck-Schuchardt, Hohenbrunn, Germany.

11. The temperature of the isopropyl alcohol bath was monitored by a cold finger device TK-300, Fryka Kältetechnik, Germany.

12. Sodium borohydride (NaBH_4) was obtained in 100-g samples (>97%) from Fluka Feinchemikalien GmbH, Neu-Ulm, Germany.

13. Hydrogen chloride, passed through a Sicapent® (E. Merck) drying tube, was fed into 500 mL of methanol (Note 10) over a period of 15 min at 0°C . The titer of the solution (7.5 N) was determined by titration with 1.0 N sodium hydroxide, Titriplex Merck-Schuchardt, Hohenbrunn, Germany against phenolphthalein as indicator.

14. The checkers found that pH indicator paper (sensitivity ± 1 pH unit) can also be used to monitor the acidity of the solution to pH 3.

15. GLC analysis (see Note 9 for conditions): $R_t = 8.3$ min, content of **2** >98%. For further purification the submitters find that the product can be distilled under reduced pressure through a 35-cm, silver-plated Vigreux column with 6-cm outer and 2-cm inner diameter (bp = $65\text{--}67^\circ\text{C}$, 0.001 mbar, 0.0007 mm); purity from GLC analysis >99.5%). The spectroscopic data of 3-nitropropanol are as follows: ^{13}C NMR (125

MHz, CDCl_3) δ : 29.8, 58.9, 72.6; ^1H NMR (500 MHz, CDCl_3) δ : 2.24 (tt, 2 H, $J = 5.8, 6.8$), 2.56 (bt, 1 H, $J = 4.6$), 3.73 (dt, 2 H, $J = 4.6, 5.8$), 4.55 (t, 2 H, $J = 6.8$); IR (CHCl_3) cm^{-1} : 3620, 3424, 2939, 2891, 1552, 1433, 1382; mass spectrum (CI) m/z 106.0503 [$\text{C}_3\text{H}_8\text{NO}_3$ ($M+1$) requires 106.0504] 106 (base), 88.

16. Trimethyl orthoformate (>97%) was obtained from Fluka Feinchemikalien GmbH, Neu-Ulm, Germany and distilled prior to use, bp 101°C .

17. *p*-Toluenesulfonic acid monohydrate (99%) was obtained from Fluka Feinchemikalien GmbH, Neu-Ulm, Germany.

18. The progress of the reaction was monitored by TLC: R_f (3-nitropropanal) = 0.35, R_f (3-nitropropanal dimethyl acetal) = 0.53, Kieselgel 60 F_{254} , Merck-Schuchardt, Hohenbrunn, Germany; eluent: ethyl acetate/hexane (3:7).

19. Charcoal p.a., obtained from Merck-Schuchardt, Hohenbrunn, Germany, was used to decolorize the dark brown solution.

20. GLC analysis (see Note 9 for conditions): $R_t = 12.9$ min, content of **3** >99%. The spectroscopic data of 3-nitropropanal dimethyl acetal **3** are as follows: ^{13}C NMR (125 MHz, CDCl_3) δ : 30.5, 54.0, 71.2, 101.9; ^1H NMR (500 MHz, CDCl_3) δ : 2.31 (dt, 2 H, $J = 5.4, 6.8$), 3.37 (s, 6 H), 4.46 (t, 2 H, $J = 6.8$), 4.48 (t, 1 H, $J = 5.4$); IR (CHCl_3) cm^{-1} : 2938, 2837, 1556, 1447, 1378; mass spectrum (CI) m/z 150.0761 [$\text{C}_5\text{H}_{12}\text{NO}_4$ ($M+1$) requires 150.0766] 118 (base), 150.

21. From **1**, various other acetals are available under standard conditions, cf. Section 3 (Discussion). For example, following the described procedure, submitters indicate that 3-nitropropanal diethyl acetal is prepared by reaction of 30.9 g (0.300 mol) of 3-nitropropanal, 53.4 g (0.360 mol) of triethyl orthoformate, and 1.0 g of *p*-toluenesulfonic acid monohydrate in 100 mL of ethanol; yield: 44.5 g (84%). GLC analysis (see Note 9 for conditions): $R_t = 14.5$ min, content >99.5%. The spectroscopic data of 3-nitropropanal diethyl acetal are as follows: ^{13}C NMR (125 MHz, CDCl_3) δ : 15.2, 31.5, 62.6, 71.4, 100.0; ^1H NMR (500 MHz, CDCl_3) δ : 1.21 (t, 6 H, $J = 7.0$), 2.30

(dt, 2 H, J = 5.3, 6.8), 3.51 (dq, 2 H, J = 7.0, 9.3), 3.68 (dq, 2 H, J = 7.0, 9.3), 4.49 (t, 2 H, J = 6.8), 4.61 (t, 1 H, J = 5.3).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995 and "Neue Datenblätter für gefährliche Arbeitsstoffe nach der Gefahrstoffverordnung", Welzbacher, U. (Ed.); WEKA Fachverlage, Kissing, 1991.

3. Discussion

This procedure describes the preparation of 3-nitropropanal, **1**, employing the rarely encountered 1,4-addition of ambident nitrite ion with its "softer" N-atom,² and further transformations of **1**, as reported earlier.³ A similar preparation of 3-nitrobutanal from crotonaldehyde (3-butenal) is known,⁴ as well as analogous additions to α,β -enones.² The reduction of **1** to the alcohol **2**, originally carried out with borane-dimethyl sulfide (BMS),³ is now more conveniently and economically done with sodium borohydride. The acetalization of **1** to yield the dimethyl acetal **3** is based on our earlier report.³

Two further preparations of 3-nitropropanal **1** have been claimed in the literature: by treatment of 1-chloro-3-nitro-2-propanol with potassium hydroxide,⁵ and by reaction of the 4-isopropyl-2-oxazolin-5-one anion with nitroethene.⁶ These alternate methods are less suited and less economic for the preparation of 3-nitropropanal **1** on a multigram scale.

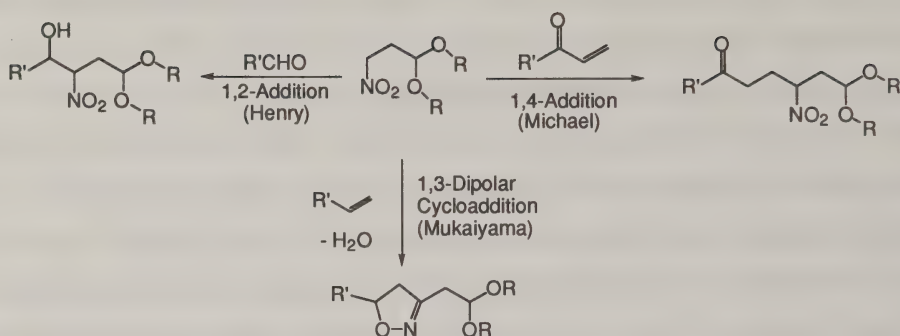
Procedures for the preparation of the acetals of 3-nitropropanal **1**⁷ have been reported from acrolein, by addition of hydrogen bromide in the presence of the

corresponding alcohol (diol)⁸ followed by bromide/nitrite exchange.⁹ 3-Nitropropanol has been obtained similarly from 3-iodo- or 3-bromopropanol with silver nitrite¹⁰ and by reduction of 3-nitropropionic acid with diborane,¹¹ or better, with borane-dimethyl sulfide (BMS).³ The use of 3-nitropropionic acid as a starting material is hampered by the fact that the common precursor, β -propiolactone, is toxic and mutagenic (LD₅₀ 50 mg, oral, rat; carcinogenic group III, <1-0.1%);¹² its fumes or aerosols inflame the skin, and on inhalation it can produce pulmonary edema.¹³

Aliphatic nitro compounds are versatile building blocks and intermediates in organic synthesis,^{14,15} cf. the overview given in the *Organic Syntheses* preparation of nitroacetaldehyde diethyl acetal.¹⁶ For example, Henry and Michael additions, respectively, lead to 1,2- and 1,4-difunctionalized derivatives.¹⁴⁻¹⁸ 1,3-Difunctional compounds, such as amino alcohols or aldols are accessible from primary nitroalkanes by dehydration/1,3-dipolar nitrile oxide cycloaddition with olefins (Mukaiyama reaction),¹⁹ followed by ring cleavage of intermediate isoxazolines by reduction or reduction/hydrolysis.^{20,21}

For synthesis of more complex target molecules by these strategies, nitroalkanes with additional O-functions are often required. Specifically, the above CC-forming additions lead to a variety of 1,3,4-, 1,3,5- and 1,3,6-functionalized structures, as shown with **3** (or nitropropyl ethers, from **2**).

Scheme 1



Examples for the use of acetals such as **3**, of 3-nitropropanal (**1**), and of 3-nitropropanol (**2**) or its O-protected derivatives are given in the references.²²⁻²⁴ A recent, notable application from this group is a short, high-yield synthesis of L-acosamine,²⁵ the arabino isomer of 3-amino-2,3,6-trideoxyhexoses that form part of many antitumor aminoglycoside antibiotics.²⁶

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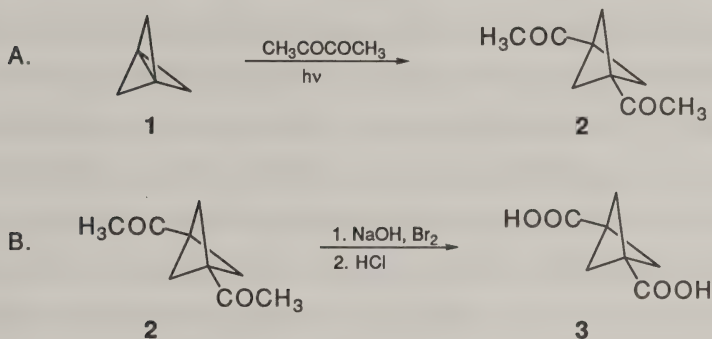
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- 3-Nitropropanal: Propanal, 3-nitro- (9); (58657-26-4)
- 3-Nitropropanol: 1-Propanol, 3-nitro- (8,9); (25182-84-7)
- 3-Nitropropanal dimethyl acetal: Propane, 1,1-dimethoxy-3-nitro- (10); (72447-81-5)
- Sodium nitrite: Nitrous acid sodium salt (8,9); (7632-00-0)
- Acrolein (8): 2-Propenal (9); (107-02-8)
- Sodium borohydride; sodium tetrahydroborate: Borate(1-), tetrahydro-, sodium (8,9); (16940-66-2)
- Methyl orange: Benzenesulfonic acid, p-[[p-(dimethylamino)phenyl]azo]-, sodium salt (8); Benzenesulfonic acid, 4-[[4-(dimethylamino)phenyl]azo]-, sodium salt (9); (547-58-0)
- Trimethyl orthoformate: Orthoformic acid, trimethyl ester (8); Methane, trimethoxy- (9); (149-73-5)
- p-Toluenesulfonic acid monohydrate (8); Benzenesulfonic acid, 4-methyl-, monohydrate (9); (6192-52-5)
- 3-Nitropropanal diethyl acetal: Propane, 1,1-diethoxy-3-nitro- (12); (107833-73-8)
- Triethyl orthoformate: Orthoformic acid, triethyl ester (8); Ethane, 1,1',1''-[methylidynetris(oxy)]tris- (9); (122-51-0)

**PHOTOCHEMICAL SYNTHESIS OF BICYCLO[1.1.1]PENTANE-
1,3-DICARBOXYLIC ACID**



Submitted by Michael D. Levin,¹ Piotr Kaszynski,² and Josef Michl.¹

Checked by Michelle Pacholec and Steven Wolff.

1. Procedure

A. *1,3-Diacetylbicyclo[1.1.1]pentane (2)*. [1.1.1]Propellane is generated from 50 g (0.167 mol) of 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (Note 1) in pentane (Note 2) according to the procedure of Lynch and Dailey.³ To the solution of [1.1.1]propellane, **1** (Note 3), is added 15 mL of freshly distilled 2,3-butanedione and the mixture is irradiated with a 450 W medium pressure UV lamp (Ace Glass Co, catalog no. 7825-34) at $-10 \pm 5^\circ\text{C}$ for 8 hr (Note 4). Solvents are evaporated on a rotary evaporator. The resulting crystalline material is washed three times with cold 2:1 pentane:diethyl ether to give 16.95 g of 1,3-diacetylbicyclo[1.1.1]pentane (**2**) (Note 5). Another 1 g of the diketone is obtained upon concentration and crystallization of the pentane/diethyl ether rinses. Thus the total yield of **2** is 17.95 g [70% from 1,1-

dibromo-2,2-bis(chloromethyl)cyclopropane], mp 67.5-69°C (lit.⁴ mp, 67-69°C) (Note 6).

B. Bicyclo[1.1.1]pentane-1,3-dicarboxylic acid (3). A 1-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, addition funnel, and thermometer is charged with a solution of 43.3 g (1.08 mol) of sodium hydroxide in 315 mL of water and 25.5 mL (79.1 g, 0.495 mol) of bromine. The mixture is cooled to 0°C. A solution of the diketone (10 g, 0.066 mol) obtained in Part A in 36 mL of dioxane is added dropwise at such a rate that the temperature does not exceed 3°C (Note 7). After the addition is finished, the reaction mixture is stirred for 1 hr at 0°C, then overnight at room temperature. Sodium bisulfite (1.8 g) is added and the solution is extracted with chloroform (3 x 50 mL). Subsequently, 36 mL of concd hydrochloric acid is added to the aqueous layer. After the acidified solution is cooled to room temperature, the mixture is continuously extracted with diethyl ether for 50 hr (Note 8) in an extraction apparatus. Evaporation of ether from the extract yields 9.68 g (94.5% from diketone 2) of pure diacid **3**, mp 302-305°C, with decomposition [lit.⁴ mp, 305°C (d)] (Note 9).

2. Notes

1. 1,1-Dibromo-2,2-bis(chloromethyl)cyclopropane was purchased from the Aldrich Chemical Company, Inc. It can be synthesized from 3-chloro-2-chloromethyl-1-propene, available from the Aldrich Chemical Company, Inc., by phase-transfer dibromocyclopropanation.^{3,5,6}

2. Pentane (98% grade) was obtained from Acros Organics and used without further purification.

3. The solution of [1.1.1]propellane should be warmed to -20-15°C to avoid crystallization of the 2,3-butanedione (which may not redissolve during the course of the irradiation).

4. It is recommended that the NMR spectrum of the reaction mixture be measured before discontinuing the irradiation. As long as any signal of [1.1.1]propellane (δ 2.0 ppm) is present, the irradiation should be continued.

5. The pentane-ether washes remove a yellow color from the crude product.

6. Spectral data were as follows: ^1H NMR δ : 2.14 (s, 6 H), 2.24 (s, 6 H); ^{13}C NMR δ : 26.6, 43.3, 52.0, 205.6; IR (KBr) cm^{-1} : 1699. MS 152 (1, M^+), 137 (11), 109 (43), 95 (10), 43 (100), 39 (25); HRMS for $\text{C}_9\text{H}_{12}\text{O}_2$ calcd 152.0837, found 152.0835. Anal. Calcd for $\text{C}_9\text{H}_{12}\text{O}_2$: C, 71.02; H, 7.95. Found: C, 71.01; H, 7.97.

7. Cooling of the reaction flask with an ice-salt or circulating bath held at -10°C helps to speed up the addition process.

8. Most of the product is extracted in the first 10 hr.

9. Spectral data were as follows: ^{13}C NMR (acetone d_6) δ : 38.1, 53.0, 170.6; IR (KBr) cm^{-1} : 3017, 1698. Anal. Calcd for $\text{C}_9\text{H}_8\text{O}_4$: C, 53.85; H, 5.16. Found: C, 53.43; H, 5.30.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described above is an improved version of the one published by Kaszynski and Michl.⁴ [1.1.1]Propellane is a recently reviewed⁷ useful precursor for the synthesis of bicyclo[1.1.1]pentanes by radical addition across the central bond, followed by further transformations of the bridgehead substituents.^{4,8} Under suitable conditions, one can obtain mixtures of [n]staffanes [oligomeric bicyclo[1.1.1]pentanes],

which have been isolated in rapidly decreasing yields up to $n = 5$.^{5,8} A review of their chemistry has appeared.⁹

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9. Kaszynski, P.; Michl, J. *Adv. Strain Org. Chem.* **1995**, *4*, 283-331.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Bicyclo[1.1.1]pentane-1,3-dicarboxylic acid (9); (56842-95-6)

1,3-Diacetylbicyclo[1.1.1]pentane: Ethanone, 1,1'-(bicyclo[1.1.1]pentane-1,3-diyl)bis-
(12); (115913-30-9)

[1.1.1]Propellane: Tricyclo[1.1.1.0^{1,3}]pentane (9); (35634-10-7)

1,1-Dibromo-2,2-bis(chloromethyl)cyclopropane: Cyclopropane, 1,1-dibromo-2,2-
bis(chloromethyl)- (11); (98577-44-7)

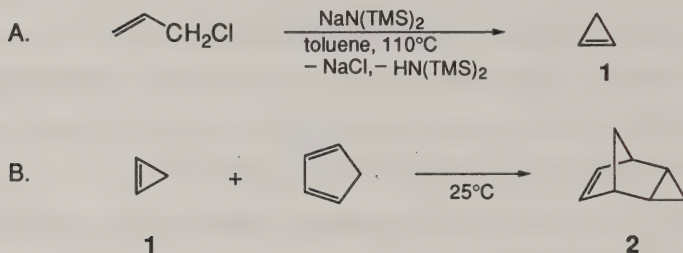
2,3-Butanedione (9); (431-03-8)

Bromine (8,9); (7726-95-6)

3-Chloro-2-(chloromethyl)-1-propene: 1-Propene, 3-chloro-2-(chloromethyl)- (8,9);
(1871-57-4)

CYCLOPROPENE: A NEW SIMPLE SYNTHESIS AND ITS DIELS-ALDER REACTION WITH CYCLOPENTADIENE

(Tricyclo[3.2.1.0^{2,4}]oct-6-ene, (1 α ,2 α ,4 α ,5 α)-)



Submitted by Paul Binger,¹ Petra Wedemann,¹ and Udo H. Brinker.²

Checked by Wenyong Wang and Amos B. Smith, III.

1. Procedure

A. *Cyclopropene* (1). A 250-mL, three-necked flask is equipped with a 25-mL dropping funnel, a Dimroth-type reflux condenser (Note 1), an immersed thermometer, a magnetic stirring bar, and a silicon oil gas bubbler with a short connection to the inlet tube of a cold trap (ampule). Argon flow (Note 2) is introduced from the top of the condenser. The flask is charged with sodium bis(trimethylsilyl)amide (Notes 3, 4) (35.05 g, 0.192 mol), which is dissolved in toluene (150 mL) (Note 5). The resulting solution is brought to a vigorous reflux (Note 6) at which time allyl chloride (Notes 7, 8) (13.8 mL, 0.169 mol) is added from the dropping funnel over a period of 45-60 min (Note 9). Cyclopropene (1) emerges from the flask and is condensed through the inlet tube into an ampule at -80°C. After an additional 30 min at reflux, 2.6 g (d = ca. 0.7 g/mL) (yield 39 %) of cyclopropene (1) is collected as a colorless liquid (purity > 95%)

containing only traces of allyl chloride as determined by ^1H NMR spectroscopy at -80°C (Note 10).

B. Reaction of cyclopropene (1) with cyclopentadiene. A 50-mL, one-necked flask equipped with a rubber septum and a stirring bar is charged with pentane (10 mL) (Note 11) and cooled to -80°C , whereupon cyclopentadiene (3.81 g, 4.76 mL, 0.058 mol) (Note 12) is added. A 25-mL flask is equipped with a rubber septum and charged with pentane (10 mL). The pentane is cooled to -80°C , then transferred via cannula into the cold trap (ampule) containing cyclopropene (1) (2.1 g, 0.052 mol). The resulting cyclopropene solution is quickly transferred through a short capillary (steel, 1 mm i.d.) to the cyclopentadiene solution (Note 13) using a positive pressure of argon. The reaction mixture is allowed to warm to room temperature within 2 hr. The resulting colorless solution is distilled via a short-path still. At 125°C , 2.80 g of endo-tricyclo[3.2.1.0^{2,4}]oct-6-ene (2) is collected. A second fraction furnished 1.16 g, providing a combined yield of 3.96 g (72 %) of 2; the purity is >99% as determined from its ^1H and ^{13}C NMR spectra (Note 14).

2. Notes

1. An internal water-cooled coil allows for efficient condensation of low-boiling vapors and prevents condensation on the outside, which might seep into joints. The checkers used an Allihn condenser.

2. A stream of argon is added after the condenser is in place to drive the cyclopropene into the cold trap. If the argon stream is too strong, cyclopropene will be blown out of the cold trap, thereby affecting the yield.

3. Sodium bis(trimethylsilyl)amide is commercially available from Aldrich Chemical Company, Inc., or Fluka Chemical Corp., but can be prepared according to reference 3.

4. Sodium bis(trimethylsilyl)amide was weighed in an air bag or glove box to minimize exposure to the air and moisture.
5. Toluene (Overlack) was dried over Na/K alloy and freshly distilled before use.
6. The oil bath should be kept between 140°C and 150°C.
7. Allyl chloride (98%, Fluka Chemical Corp.) was freshly distilled before use.
8. Optimal yields were obtained when using 0.85-0.90 equiv of allyl chloride.^{8a}
9. If the allyl chloride is added too quickly, some of the cyclopropene is not condensed and is blown out of the system. In addition, allyl chloride will condense in the cold trap, affecting the purity of the cyclopropene.
10. The following spectra were obtained: ¹H NMR (500 MHz, toluene-d₈, -80°C, round-bottom tube, 5-mm wide) δ: 1.18-1.19 (m, 2 H), 6.69-6.70 (m, 2 H); ¹³C NMR (125 MHz, toluene-d₈, -80°C) δ: 3.0, 108.5 (2C).
11. Pentane (> 98%, Aldrich Chemical Company, Inc.) was distilled before use.
12. Cyclopentadiene (purity > 99%) was obtained by cracking the dimer (Aldrich Chemical Company, Inc.) at 180°C.
13. The NMR spectrum recorded at -80°C showed that no reaction takes place (even after 24 hr).
14. The spectra were as follows: ¹H NMR (500 MHz, CDCl₃) δ: 0.37-0.39 (m, 1 H), 0.57-0.62 (m, 1 H), 1.33-1.36 (m, 2 H), 1.69-1.71 (m, 1 H), 1.80-1.82 (m, 1 H), 2.77 (s, 2 H), 5.70-5.71 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ: 12.3 (2C), 17.0, 42.3 (2C), 63.6, 130.4 (2C).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

A variety of diverse synthetic methods have been employed for the preparation of cyclopropene (**1**).⁴ Schlatter^{5a} and Demjanov and Dojarenko^{5b} pyrolyzed cyclopropyltrimethylammonium hydroxide at 320°C using platinized asbestos as the catalyst. About equal amounts of cyclopropene (**1**) and cyclopropyldimethylamine are formed, contaminated with some dimethyl ether and ethylene. Treatment with dilute hydrochloric acid removed the amine from the gas stream and **1** was separated from the other products by gas chromatography. Alder-Rickert cleavage of the Diels-Alder adduct formed from cycloheptatriene and dimethyl acetylenedicarboxylate resulted only in the formation of a polymer and trace amounts of **1**.⁶ A simple approach by Closs and Krantz⁷ based on the synthesis of 1-methylcyclopropene⁸ involved the addition of allyl chloride to a suspension of sodium amide in mineral oil at 80°C. Under the conditions employed, **1** could readily escape from the reaction mixture.⁷ Though a number of variations were tried, the yield of **1** never exceeded 10%.

From a preparative point of view, previous attempts at preparing cyclopropene (**1**) are either very laborious or low yielding. Over the last 25 years, the submitters have developed simple syntheses for substituted cyclopropenes on a multigram scale.^{4a,8} Here they present their efforts towards an improved synthesis of the parent compound **1**.

When allyl chloride (Notes 7, 8, 9) was dropped into a solution of sodium bis(trimethylsilyl)amide (Notes 3, 4) in boiling toluene (Notes 5, 6), cyclopropene (**1**) could be isolated in a trap/ampule at -80°C.⁹ Compared with the published procedure,⁷ these conditions proved superior, affording **1** in about 40% yield. Furthermore, as could be established by NMR spectroscopy at -80°C, the cyclopropene (**1**) was nearly pure (>95%) (Note 10), containing only traces of allyl chloride. Compound **1**, prepared in this manner, was found to be stable in toluene

solution at -78°C for at least 1 week. Upon warming to -30°C, **1** begins to oligomerize (NMR control).

When **1** was reacted with cyclopentadiene (Note 12) at -80°C or -30°C, no reaction took place, as determined by NMR spectroscopy. At room temperature, however, the Diels-Alder reaction afforded exclusively endo-tricyclo[3.2.1.0^{2,4}]oct-6-ene (**2**) in 70% yield.^{6,7,9}

Acknowledgments U.H.B. thanks the State University of New York at Binghamton for a sabbatical leave and those at the Max-Planck-Institut für Kohlenforschung for their generous hospitality.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Cyclopropene (8,9); (2781-85-3)

Cyclopentadiene: 1,3-Cyclopentadiene (8,9); (542-92-7)

Sodium bis(trimethylsilyl)amide: Disilazane, 1,1,1,3,3,3-hexamethyl-, sodium salt (8);

Silamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, sodium salt (9); (1070-89-9)

Allyl chloride: Propene, 3-chloro- (8); 1-Propene, 3-chloro- (9); (107-05-1)

endo-Tricyclo[3.2.1.0^{2,4}]oct-6-ene: Tricyclo[3.2.1.0^{2,4}]oct-6-ene, endo- (8);

Tricyclo[3.2.1.0^{2,4}]oct-6-ene, (1 α ,2 α ,4 α ,5 α)- (9); (3635-94-7)

Unchecked Procedures

Accepted for checking during the period September 1, 1998 through September 1, 1999. An asterisk (*) indicates that the procedure has been subsequently checked.

Previously, *Organic Syntheses* has supplied these procedures upon request. However, because of the potential liability associated with procedures which have not been tested, we shall continue to list such procedures but requests for them should be directed to the submitters listed.

- 2863R Bicyclopropylidene.
A. de Meijere, S. I. Kozhushkov, and T. Späth, Institut für Organische Chemie der Georg-August-Universität, Tammannstrasse 2, D-37077 Göttingen, Germany.
- 2865 Bu_3SnH -Catalyzed Barton-McCombie Deoxygenation of Alcohols: 3-Deoxy-1,2:5,6-Bis-O-(1-methylethylidene)- α -D-Ribohexofuranose.
J. Tormo and G. C. Fu, Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139.
- *2866 2-(3-Oxobutyl)cyclopentanone-2-carboxylic Acid Ethyl Ester.
J. Christoffers, Technische Universität Berlin, Institut für Organische Chemie, Sekretariat C3, Strasse des 17. Juni 135, D-10623 Berlin, Germany.
- 2868 1,2-Metallate Rearrangement: (Z)-4-(2-Propenyl)-3-octen-1-ol.
K. Jarowicki, P. J. Kocienski, and L. Qun, Department of Chemistry, University of Glasgow, Glasgow, G12 8QQ, UK.
- 2876 Synthesis of Amino Acid Ester Isocyanates: Methyl (S)-2-Isocyanato-3-phenylpropanoate.
J. H. Tsai, L. R. Takaoka, N. A. Powell, and J. S. Nowick, Department of Chemistry, University of California, Irvine, Irvine, CA 92717.
- 2880 In situ Catalytic Epoxidation of Olefins with Tetrahydrothiopyran-4-one and Oxone: 2-Methyl-2,3-diphenyloxirane.
D. Yang, Y.-C. Yip, G.-S. Jiao and M.-K. Wong, Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong.
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The index lists the names of compounds in two forms. The first is the name used commonly in procedures. The second is the systematic name according to **Chemical Abstracts** nomenclature. Both are usually accompanied by registry numbers in parentheses. Also included are general terms for classes of compounds, types of reactions, special apparatus, and unfamiliar methods.

Most chemicals used in the procedure will appear in the index as written in the text. There generally will be entries for all starting materials, reagents, intermediates, important by-products, and final products. Entries in capital letters indicate compounds appearing in the title of the preparation.

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